11-08-00

PTO/SB/05 (2/98)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → +

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37C F R §1 53(b))

Attorney Docket No.	PC10408A
First Named Inventor or Application Identifier	Sobolov-Jaynes
Title	COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY
Express Mail Label No.	EM292625586

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ *Fee Transmittal Form (e.g., *PTO/SB/17*)
(Submit an original, and a duplicate for fee processing)

2. ☒ Specification [Total Pages 70]
(preferred arrangement set forth below)
- Descriptive title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R&D
- Reference in Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings *(if filed)*
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. ☐ Drawing(s) *(35 U.S.C. 11.3)*[Total sheets]

4. ☐ Oath or Declaration [Total pages]
a. ☐ Newly executed (original or copy)
b. ☐ Copy from a prior application (37 CFR §1.63(d))
(for continuation/divisional with Box 17 completed)
[Note Box 5 below]
i. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference *(useable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program *(Appendix)*

7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
a. ☐ Computer Readable Copy
b. ☐ Paper Copy (identical to computer copy)
c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☒ 37 C.F.R. §3.73(b) Statement ☐ Power of Attorney *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. ☐ *Small Entity Statement(s) *(PTO/SB/09-12)* ☐ Statement filed in prior application, Status still proper and desired
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. ☒ Other: Priority Claim
U.S. Serial No. 60/164,692, filed Nov. 10, 1999

*NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*
☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: /

Prior application information: Examiner _____ Group/Art Unit: _____

18. CORRESPONDENCE ADDRESS

☐ *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* **or** ☒ *Correspondence address below*

Name	Paul H. Ginsburg				
Address	Pfizer Inc				
Address	235 East 42nd Street, 20th Floor				
City	New York	State	New York	Zip Code	10017-5755
Country	United States Of America	Telephone	(212)573-2369	Fax	(212)573-1939

NAME (Print/type)	A. David Joran	Registration No. (Attorney/Agent)	37,858
Signature		Date	November 7, 2000

UTILITY TRANSMITTAL PTO SB 05, 3/99, (1/1)

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PTO/SB/17(2/98)
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FEE TRANSMITTAL

Patent fees are subject to annual revision on October 1. These are the fees effective October 1, 1997.

*Small Entity payments **must** be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.*

See 37 C.F.R. §§ 1.27 and 1.28.

Total Amount of Payment ($)1,016.00

Complete if Known	
Application Number	Not Yet Known
Filing Date	Concurrently Herewith
First Named Inventor	Sobolov-Jaynes et al
Examiner Name	Not Yet Known
Group/Art Unit	Not Yet Known
Attorney Docket No.	PC10408AADJ

METHOD OF PAYMENT (check one)

1. ☒ The commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 16-1445

Deposit Account Name: Pfizer Inc.

☒ Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17.

☐ Charge the Issue Fee Set in 37 C.F.R. § 1.18 at the Mailing of the Notice of Allowance.

2. ☐ **Payment Enclosed:**

☐ Check ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	710.00
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 710.00

2. EXTRA CLAIM FEES

			Extra Claims	Fee from below		Fee Paid
Total Claims	22	-20**=	2	18	=	36.00
Independent Claims	1	- 3**=	0	X 80	=	0.00
Multiple Dependent				270	=	270.00

** or number previously paid, if greater; For Reissues, see below

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	80	209	40	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 306.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late fee or oath	
127	50	227	25	Surcharge–late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Statement	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR 1.129(b))	
Other Fee (specify)					
Other Fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)

SUBMITTED BY				Complete (if Applicable)	
Type or Printed Name	A. David Joran			Reg. Number	37,858
Signature		Date	11-7-00	Deposit Account User ID	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: SUSAN B. SOBOLOV-JAYNES	:
APPLICATION NO.: Not Yet Known	:
FILING DATE: Concurrently Herewith	:
TITLE: COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY	:

Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Sir:

Preliminary Amendment

Prior to examination on the merits, please amend the above-identified application as follows.

In the Specification:

Page 1, before first line insert:

- - - This application claims the benefit of provisional application Serial No. 60/164,692, filed November 10, 1999. - - -.

REMARKS

The subject application is a non-provisional patent application based on copending provisional application Serial No. 60/164,692, filed November 10, 1999. The present amendment does not introduce new matter, and entry is hereby requested.

Applicants believe the subject application is in proper form, and expeditious examination is respectfully solicited.

Date: Nov. 7, 2000

Respectfully submitted,

A. David Joran
Attorney for Applicant
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COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY

Background of the Invention

The present invention relates to a method of treating depression or anxiety in a mammal, including a human, by administering to the mammal a CNS-penetrant NK-1 receptor antagonist (e.g., a substance P receptor antagonist) in combination with an antidepressant or an anxiolytic agent. It also relates to pharmaceutical compositions containing a pharmaceutically acceptable carrier, a CNS-penetrant NK-1 receptor antagonist and an anxiolytic agent or antidepressant.

Major depression is characterized by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes also occur, especially in severe or "melancholic" depression. These include insomnia or hypersomnia, anorexia and weight loss (or sometimes overeating), decreased energy and libido, and disruption of normal circadian rhythms of activity, body temperature, and many endocrine functions.

Treatment regimens commonly include the use of tricyclic antidepressants, monoamine oxidase inhibitors, some psychotropic drugs, lithium carbonate, and electroconvulsive therapy (ECT) (see R. J. Baldessarini in *Goodman & Gilman's The Pharmacological Basis of Therapeutics,* 9th Edition, Chapter 19, McGraw-Hill, 1996 for a review). More recently, new classes of antidepressant drugs are being developed including selective serotonin re-uptake inhibitors (SSRIs), specific monoamine re-uptake inhibitors and 5-HTIA receptor agonists, antagonists and partial agonists.

Anxiety is an emotional condition characterized by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating and tremor. It is a normal emotion but when it is severe and disabling it becomes pathological.

Anxiety disorders are generally treated using benzodiazepine sedative-antianxiety agents. Potent benzodiazepines are effective in panic disorder as well as in generalized anxiety disorder, however, the risks associated with drug dependency may limit their long-term use. 5-HT_{IA} receptor partial agonists also have useful anxiolytic and other psychotropic activity, and less likelihood of sedation and dependence (see R. J. Baldessarini in *Goodman & Gilman's Tite Pharmacological Basis of Therapeutics,* 9th Edition, Chapter 18, McGraw-Hill, 1996 for a review).

Summary Of The Invention

The present invention relates to a pharmaceutical composition for the treatment of anxiety or depression comprising: (a) a compound that exhibits activity as an antianxiety (i.e.,

anxiolytic) agent or an antidepressant, or a pharmaceutically acceptable salt thereof; (b) a CNS-penetrant NK-1 receptor antagonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, anxiety or depression.

This invention also relates to a method of treating anxiety or depression in a mammal, comprising administering to said mammal, respectively, an anxiolytic or antidepressant effective amount of a pharmaceutical composition comprising: (a) a compound that exhibits activity as, respectively, an anxiolytic agent or an antidepressant, or a pharmaceutically acceptable salt thereof; (b) a CNS-penetrant NK-1 receptor antagonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, anxiety or depression.

This invention also relates to a method of treating anxiety or depression in a mammal, comprising administering to said mammal: (a) a compound that exhibits activity as, respectively, an anxiolytic agent or an antidepressant, or a pharmaceutically acceptable salt thereof; and (b) a CNS-penetrant NK-1 receptor antagonist or pharmaceutically acceptable salt thereof; wherein the active agents "a" and "b" above are present in amounts that render the combination of the two agents effective in treating, respectively, anxiety or depression.

It will be appreciated that when using a combination method of the present invention, referred to immediately above, both the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anti-anxiety agent will be administered to a patient within a reasonable period of time. The compounds may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms that are taken simultaneously. The term combination, as used above, also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, the antidepressant or anxiolytic agent may be administered as a tablet and then, within a reasonable period of time, the CNS-penetrant NK-1 receptor antagonist may be administered either as an oral dosage form such as a tablet or a fast-dissolving oral dosage form. By a "fast dissolving oral formulation" is meant, an oral delivery form which when placed on the tongue of a patient, dissolves within about seconds.

The compositions of the present invention that contain an NK-1 receptor antagonist and an antidepressant are useful for the treatment of depression. As used herein, the term "depression" includes depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias, seasonal

affective disorder, or bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder.

Other mood disorders encompassed within the term "depression" include dysthymic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood, disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

The compositions of the present invention that contain an NK-1 receptor antagonist and an anxiolytic agent are useful for the treatment of anxiety. As used herein, the term "anxiety" includes anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders.

"Generalized anxiety" is typically defined as an extended period (e.g. at least six months) of excessive anxiety or worry with symptoms on most days of that period. The anxiety and worry is difficult to control and may be accompanied by restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep.

"Panic disorder" is defined as the presence of recurrent panic attacks followed by at least one month of persistent concern about having another panic attack. A "panic attack" is a discrete. period in which there is a sudden onset of intense apprehension, fearfulness or terror. During a panic attack, the individual may experience a variety of symptoms including palpitations, sweating, trembling, shortness of breath, chest pain, nausea and dizziness. Panic disorder may occur with or without agoraphobia.

"Phobias" includes agoraphobia, specific phobias and social phobias. "Agoraphobia" is characterized by an anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of a panic attack. Agoraphobia may occur without history of a panic attack. A "specific phobia" is characterized by clinically significant anxiety provoked by feared object or situation. Specific phobias include the following subtypes: animal type, cued by animals or insects; natural environment type, cued by objects in the natural environment, for example storms, heights or water; blood-injection-injury type, cued by the sight of blood or an injury or by seeing or receiving an injection or other invasive medical procedure; situational type, cued by a specific situation such as public transportation, tunnels, bridges, elevators, flying, driving or enclosed spaces; and other type where fear is cued by other stimuli. Specific phobias may also be referred to as simple phobias. A "social phobia" is characterized by clinically significant anxiety provoked by exposure to certain types of social or performance circumstances. Social phobia may also be referred to as social anxiety disorder.

Other anxiety disorders encompassed within the term "anxiety" include anxiety disorders induced by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, anxiolytics and other substances, and adjustment disorders with anxiety or with mixed anxiety and depression.

Anxiety may be present with or without other disorders such as depression in mixed anxiety and depressive disorders. The compositions of the present invention are therefore useful in the treatment of anxiety with or without accompanying depression.

The compositions of the present invention are especially useful for the treatment of depression or anxiety where the use of an antidepressant or anxiolytic agent, respectively, is generally prescribed. By the use of a combination of a CNS-penetrant NK-1 receptor antagonist and an antidepressant or anxiolytic agent in accordance with the present invention, it is possible to treat depression and/or anxiety in patients for whom conventional antidepressant or antianxiety therapy might not be wholly successful or where dependence upon the antidepressant or antianxiety therapy is prevalent.

Suitable classes of antidepressant agents that may be used in the present invention include norepinephrine re-uptake inhibitors, selective serotonin re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline re-uptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical antidepressants.

Another class of antidepressant agents that may be used in the present invention are noradrenergic and specific serotonergic antidepressants (NaSSAs). A suitable example of a NaSSA is mirtazapine.

Suitable norepinephrine re-uptake inhibitors that may be used in the present Invention include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Another norepinephrine re-uptake inhibitor that may be used in the present invention is reboxetine.

Suitable selective serotonin re-uptake inhibitors that may be used in the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

Suitable monoamine oxidase inhibitors that may be used in the present invention include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase that may be used in the present invention include: moclobemide, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline re-uptake inhibitors that may be used in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists that may be used in the present invention include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/l3661, WO 94/13676 and WO 94/13677.

Suitable atypical antidepressants that may be used in the present invention include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof Another suitable atypical antidepressant is sibutramine.

Other antidepressants that may be used in the present invention include adinazolam, alaproclate, amineptine, amitriptyline/chlordiazepoxide combination, atipamezole, azamianserin, bazinaprine, befuraline, bifemelane, binodaline, bipenamol, brofaromine bupropion, caroxazone, ericlamine, cianopramine, cimoxatone, citalopram, clemeprol, clovoxamine, dazepinil, deanol, demexiptiline, dibenzepin, dothiepin, droxidopa, enefexine, estazolam, etoperidone, femoxetine, fengabine, fezolamine, fluotracen, idazoxan, indalpine, indeloxazine, iprindole, levoprotiline, litoxetine, lofepramine, medifoxamine, metapramine, metralindole, mianserin, milnacipran, minaprine, mirtazapine, montirelin, nebracetam, nefopam, nialamide, nomifensine, norfluoxetine, orotirelin, oxaflozane, pinazepam, pirlindone, pizotyline, ritanserin, rolipram, sercloremine, setiptiline, sibutramine, sulbutiamine, sulpiride, teniloxazine, thozalinone, thymoliberin, tianeptine, tiflucarbine, tofenacin, tofisopam, toloxatone, tomoxetine, veralipride, viqualine, zimelidine and zometrapine, and pharmaceutically acceptable salts thereof, and St. John's wort herb, or *Hypericuin perforatum*, or extracts thereof.

Suitable classes of anti-anxiety agent that may be used in the present invention include benzodiazepines and 5-HT_{IA} agonists or antagonists, especially 5-HT_{IA} partial agonists, and corticotropin releasing factor (CRF) antagonists. In addition to benzodiazepines, other suitable classes of antianxiety agent are nonbenzodiazepine sedative-hypnotic drugs such as zolpidem; mood-stabilizing drugs such as clobazam, gabapentin, lamotrigine, loreclezole, oxcarbamazepine, stiripentol and vigabatrin; and barbiturates.

Suitable benzodiazepines that may be used in the present invention include: alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.

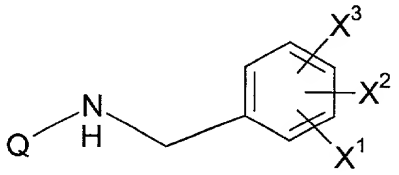
Suitable 5-HT_{1A} receptor agonists or antagonists that may be used in the present invention include, in particular, the 5-HT_{IA} receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof. An example of a compound with 5-HT_{IA} receptor antagonist/partial agonist activity is pindolol.

Suitable CRF antagonists that may be used in the present invention include those compounds described in International Patent Application Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.

Another class of anti-anxiety agent that may be used in the present invention are compound having muscarinic cholinergic activity. Suitable compounds in this class include m1 muscarinic cholinergic receptor agonists such as those compounds described in European Patent Application Nos. 0 709 093, 0 709 094 and 0 773 021, and International Patent Application No. WO 96/12711.

Another class of anti-anxiety agent that may be used in the present invention are compounds acting on ion channels. Suitable compounds in this class include carbamazepine, lamotrigine and valproate, and pharmaceutically acceptable salts thereof.

Examples of NK-1 receptor antagonists that may be used in the methods and pharmaceutical compositions of this invention are compounds of the formula

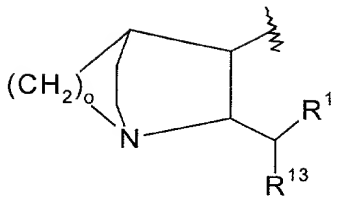


I

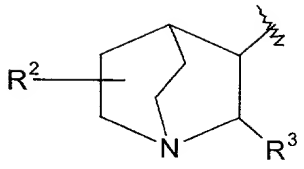
and their pharmaceutically acceptable salts, wherein X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6) alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and

Q is a group of the formula



II



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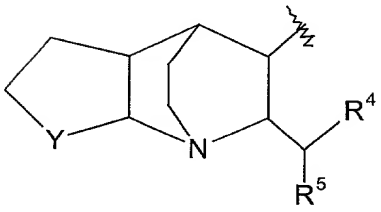

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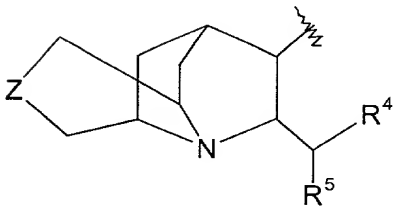

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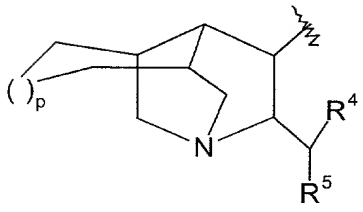
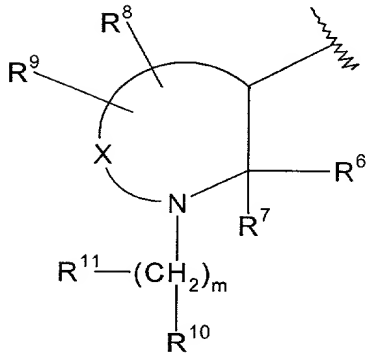
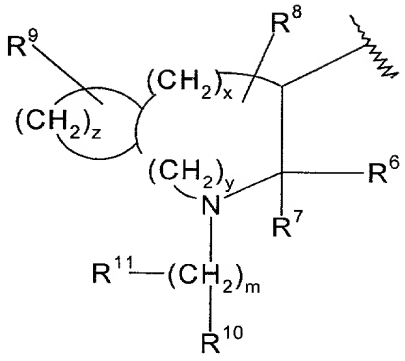


VI



VII

OR



VIII

wherein R^1 is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl

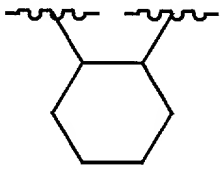
optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

R^{13} is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^1;

R^2 is hydrogen or (C_1-C_6) alkyl;

R^3 is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R^3 may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



(J)

;

Z is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

o is two or three;

p is zero or one;

R^4 is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C_1-C_3) alkoxy-carbonyl and benzyloxycarbonyl;

R^5 is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^8, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^9;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{11};

R^6 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the

phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl,(C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^7 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^6 and R^7, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^8 and R^9 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,-(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^6;

R^{10} is $NHCR^{12}$, $NHCH_2R^{12}$, $NHSO_2R^{12}$ or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9;

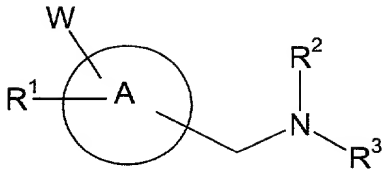
R^{11} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9; and

R^{12} is (C_1-C_6)alkyl, hydrogen, phenyl(C_1-C_6)alkyl or phenyl optionally substituted with (C_1-C_6) alkyl; and

with the proviso that (a) when m is 0, R^{11} is absent, (b) neither R^8, R^9, R^{10} nor R^{11} can form, together with the carbon to which it is attached, a ring with R^7, (c) when Q is a group of the formula VIII, R^8 and R^9 cannot be attached to the same carbon atom, and (d) when R^8 and R^9 are attached to the same carbon atom, then either each of R^8 and R^9 is independently selected from hydrogen, fluoro, (C_1-C_6) alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^8 and R^9, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached.

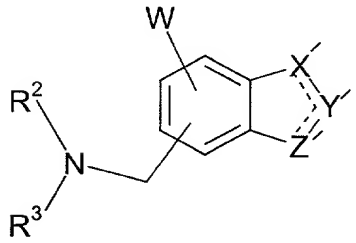
Other examples of NK-1 receptor antagonists that can be used in the methods and pharmaceutical compositions of this invention are compounds of the formula I, as defined above, with the further proviso that when neither X^1, X^2 nor X^3 is a fluorinated alkoxy group, at least one of R^1, R^3, R^4, R^5, R^6, R^7 and R^{13} is an aryl group substituted with a fluorinated alkoxy group. Such compounds are hereinafter referred to as "compounds of the formula Ia".

Other examples of NK-1 receptor antagonists that can be used in the methods and pharmaceutical compositions of this invention are compounds of the formula



IXa

or



IXb

and their pharmaceutically acceptable salts, wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the side chain containing NR^2R^3 is attached to a carbon atom of ring system A;

W is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with from one to three fluorine atoms, $-S(O)_v\text{-}(C_1\text{-}C_6)$ alkyl wherein v is zero, one or two, halo, benzyloxy or $(C_1\text{-}C_6)$alkoxy optionally substituted with from one to three fluorine atoms;

R^1 is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazolyl or thiophenyl), wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from $(C_1\text{-}C_6)$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_6)$ alkoxy optionally substituted with from one to three fluorine atoms;

the dotted lines in formula Ib indicate that one of the X'-Y' and Y'-Z' bonds may optionally be a double bond;

X' is selected from =CH-, $-CH_2$-, -O-, -S-, -SO-, $-SO_2$-, $-N(R^4)$-, -NH-, =N-, $-CH[(C_1\text{-}C_6)$alkyl]-, $=C[(C_1\text{-}C_6)$alkyl]-, $-CH(C_6H_5)$- and $=C(C_6H_5)$-;

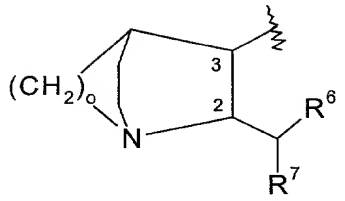
Y' is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2$-, $=C[(C_1\text{-}C_6)$alkyl]-, $-CH[(C_1\text{-}C_6)$alkyl]-, $=C(C_6H_5)$-, $-CH(C_6H_5)$-, =N-, -NH-, $-N(R^4)$-, =C(halo)-, $=C(OR^4)$-, $=C(SR^4)$-, $=C(NR^4)$-, -O-, $=C(CF_3)$-, $=C(CH_2C_6H_5)$-, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)$- and $-CH(C_6H_5)$- may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of said $=[(C_1\text{-}C_6)$alkyl]- and $-CH[C_1\text{-}C_6)$alkyl]- may optionally be substituted with from one to three fluorine atoms;

Z' is selected from =CH-, $-CH_2$-, =N-, -NH-, -S-, $-N(R^4)$-, $=C(C_6H_5)$-, $-CH(C_6H_5)$-, $=C[(C_1\text{-}C_6)$ alkyl]- and $-CH[(C_1\text{-}C_6)$alkyl]-;

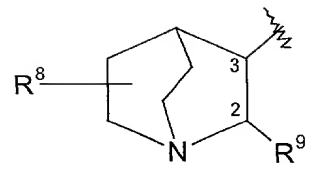
or X', Y' and Z', together with the two carbon atoms shared between the benzo ring and the X'Y'Z' ring, form a fused pyridine or pyrimidine ring;

R^2 is hydrogen or $-CO_2(C_1-C_{10})$alkyl;

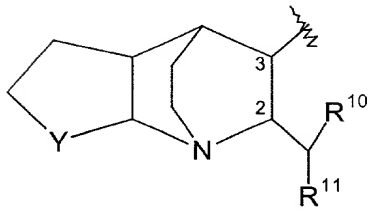
R^3 is selected from



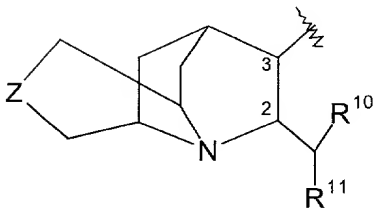
X



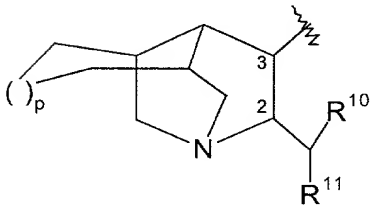
XI



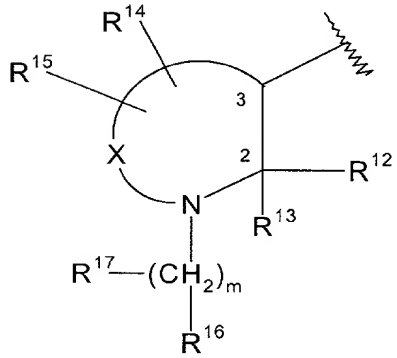
XII



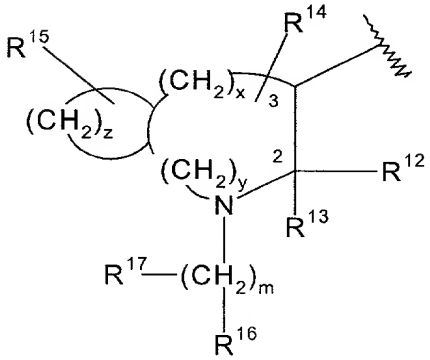
XIII



XIV

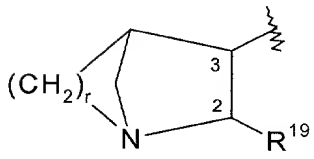


XV



XVI

and



XVII

wherein R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl, wherein said phenyl may optionally be substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and $(C_1\text{-}C_3)$ alkoxy-carbonyl;

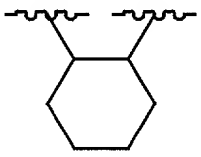
R^4 is $(C_1\text{-}C_6)$ alkyl or phenyl;

R^7 is selected from $(C_3\text{-}C_4)$ branched alkyl, $(C_5\text{-}C_6)$ branched alkenyl, $(C_5\text{-}C_7)$ cycloalkyl, and the radicals named in the definition of R^6;

R^8 is hydrogen or $(C_1\text{-}C_6)$ alkyl;

R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



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;

Z is oxygen, sulfur, amino, $(C_1\text{-}C_3)$alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

x is zero, one or two;

y is zero, one or two;

z is three, four or five;

o is two or three;

p is zero or one;

r is one, two or three;

the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbon atoms of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;

X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};

R^{12} is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6) alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^{13} is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to such point of attachment may optionally be replaced by oxygen, nitrogen or sulfur;

R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C(=O)-OH, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^{12};

R^{16} is $NHC(=O)R^{18}$, $NHCH_2R^{18}$, SO_2R^{18}, CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};

R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and

R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

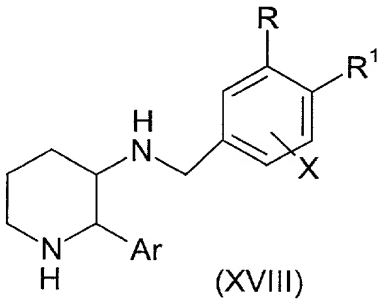
with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula XVI, R^{14} and R^{15} cannot be attached to the same

carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, $(C_1\text{-}C_6)$alkyl, hydroxy-$(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a $(C_3\text{-}C_6)$ saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} can not both be hydrogen, and (e) when R^{14} or R^{15} is attached to a carbon atom of X or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom.

The fused bicyclic nucleus of compounds of the formula IXb to which W and the -$CH_2NR^2R^3$ sidechain are attached may be, but is not limited to, one of the following groups: benzoxazolyl, benzthiazolyl, benzimidazolyl, benzisoxazolyl, benzoisothiazolyl, indazolyl, indolyl, isoquinolinyl, benzofuryl, benzothienyl, oxindolyl, benzoxazolinonyl, benzthiazolinonyl, benzimidazolinonyl, benzimidazoliniminyl, dihydrobenzothienyl-S,S-dioxide, benztriazolyl, benzthiadiazolyl, benzoxadiazolyl, and quinazolinyl.

Examples of acids that can be used to prepare pharmaceutically acceptable acid addition salts of basic NK-1 antagonists and basic compounds exhibiting antidepressant or anxiolytic properties for use in this invention are those that which form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [*i.e.*, 1,10-methylene-bis-(2-hydroxy-3- naphthoate)]salts. The chemical bases that can be used as reagents to prepare the pharmaceutically acceptable base salts of acidic NK-1 antagonists and acidic compounds exhibiting antidepressant or anxiolytic properties for use in this invention are hose which form non-toxic base salts with such compounds. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc.

Other examples of NK-1 receptor antagonists that can be used in the method and pharmaceutical compositions of this invention are compounds of the formula



(XVIII)

and their pharmaceutically acceptable salts, wherein

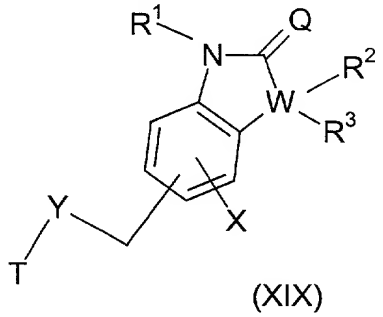
R is halo (C_1-C_8)alkyl, halo (C_2-C_8)alkenyl, halo (C_2-C_8)alkynyl or halo (C_1-C_8)alkyl substituted by hydroxy or (C_1-C_8)alkoxy; R^1 is hydrogen, halo or (C_1-C_6)alkoxy; or

R and R^1, together with the two carbon atoms shared between the benzene ring and the R and R^1, complete a fused (C_4-C_6)cycloalkyl wherein one carbon atom is optionally replaced by oxygen and wherein one or two of the carbon atoms are optionally substituted by up to five substituents selected from halo, (C_1-C_6)alkyl and halo (C_1-C_6)alkyl;

X is (C_1-C_6)alkoxy, halo (C_1-C_6)alkoxy, phenoxy or halo; and

Ar is phenyl optionally substituents by halo.

Other examples of NK-1 receptor antagonists that can be used in the methods and pharmaceutical compositions of this invention are compounds of the formula



(XIX)

and their pharmaceutically acceptable salts, wherein

W is methylene, ethylene, propylene, vinylene, -CH_2-O-,-O-CH_2-, -CH_2-S- or -S-CH_2-;

R^1, R^2 and R^3 are independently hydrogen, (C_1-C_3) alkyl, (C_1-C_3) alkoxy or halo (C_1-C_3) alkyl, provided that when W is methylene, both R^2 and R^3 are not hydrogen;

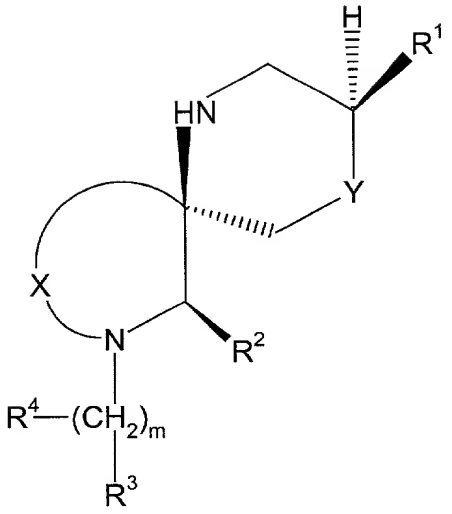
X is halo, (C_1-C_3) alkoxy, (C_1-C_3) alkoxy or (C_1-C_3) alkenyl;

Y is imino or oxy;

Q is oxygen or sulfur; and

T is (2S,3S)-2-diphenylmethylquinuclidin-3-yl,(2S,3S)-2-phenylpiperdin-3-yl or (2S,3S)-2-diphenylmethyl-1-azanorbornan-3-yl.

Other examples of NK-1 antagonists that can be used in the pharmaceutical compositions and methods of this invention are the following compounds and their pharmaceutically acceptable salts:



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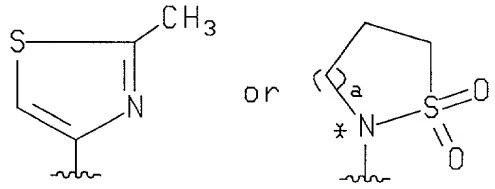
wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl,-NHC(=O)H, -NHC(=O)-(C_1-C_6) alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -$S(O)_v$-(C_1-C_{10})-alkyl wherein v is zero, one or two, -$S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, -$SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, (SO_2-(C_1-C_{10})alkyl) ((C_1-C_{10})alkyl)N wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, -N(SO_2-(C_1-C_{10})alkyl)$_2$ and (SO_2-aryl) ((C_1-C_{10})alkyl)N; and wherein the aryl moieties of said -$S(O)_v$-aryl, -O-aryl and (SO_2-aryl) ((C_1-C_{10})alkyl)N are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;

or R^1 is phenyl substituted with a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R^1;

R^2 is selected from (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from

biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;

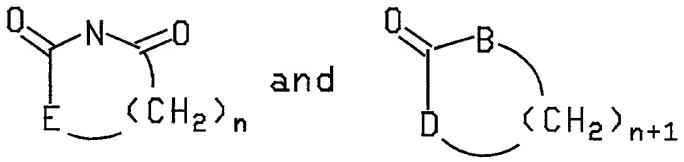
R^3 is selected from $NHC(=O)R^8$, $NHCH_2R^8$, SO_2R^8, AR^5, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;

A is CH_2, nitrogen, oxygen, sulfur or carbonyl;

R^8 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

R^4 is selected from oximino (=NOH) and the radicals set forth in the definitions of R^2, R^6 and R^7;

R^5 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said

$(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

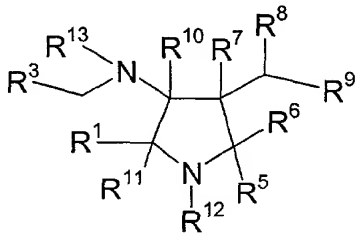
X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;

R^6 and R^7 are independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C(=O)-OH, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl- and the radicals set forth in the definition of R^2; and

Y is $(CH_2)_z$ wherein z is zero or one;

with the proviso that: (a) when A is $-(CH_2)-$ or carbonyl, R^5 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom;

Other examples of NK-1 receptor antagonists that can be used in the methods and pharmaceutical compositions of this invention include the following compounds and their pharmaceutically acceptable salts:



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wherein R^1 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)- (C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-,

-NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, phenyl, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6) alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)- -C-O-(C_1-C_6)alkyl, -C(=O)H, $-CH_2OR^{13}$, NH(C_1-C_6)alkyl-, -NHC(=O)H, $-NR^{24}$C-(C_1-C_6)alkyl and –NHC(=O)-(C_1-C_6)alkyl;

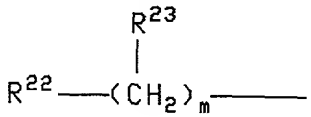
one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, (C_1-C_3)alkyl, (C_1-C_8)acyloxy(C_1-C_3)alkyl, (C_1-C_8)alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl, HC(=O)-, $R^{14}R^{15}NCO_2CH_2$-, $R^{16}OCO_2CH_2$-, (C_1-C_4)alkyl-CO_2CH_2-, -$CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2$-, $R^{19}OCO_2$-, $C_6H_5CH_2CO_2CH_2$-, $C_6H_5CO_2CH_2$-, (C_1-C_4)alkyl-CH(OH)-, $C_6H_5CH(OH)$-, $C_6H_5CH_2CH(OH)$-, CH_2halo, $R^{20}SO_2OCH_2$, -CO_2R^{16} and $R^{21}CO_2$-;

R^{10} and R^{11} are independently selected from hydrogen, (C_1-C_3) alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula



wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^{23} (as indicated by the slanted line to R^{23} which intersects the horizontal line to $(CH_2)_m$ in the above figure);

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)-alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)- (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)-alkyl-C(=O)-(C_1-C_6)alkyl, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-

C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O), (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_8)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the proviso that when R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged.

Examples of specific NK-1 receptor antagonists that can be used in the methods and pharmaceutical compositions of this invention are the following compounds and their pharmaceutically acceptable salts:

(*2S,3S*)-3-[2-methoxy-5-(2-thiazolyl)benzyl]amino-2-phenylpiperidine;

(*2S,3S*)-3-(5-(2-imidazolyl)-2-methoxybenzyl]amino-2-phenylpiperidine;

(*2S,3S*)-3-(2-methoxy-5-(2-oxopyrrolidinyl)benzyl]amino-2-phenylpiperidine;

(*2S,3S*)-3-[2-methoxy-5-(4-methyl-2-thiazolyl)benzyl]-amino-2-phenylpiperidine;

(*2S,3S*)-3-(2-methoxy-5-(1,2,3-thiadiazol-4-yl)benzyl]amino-2-phenylpiperidine;

(*2S,3S*)-(6-methoxy-2-methyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(5-(2,5-dimethyl-pyrrol-1-yl)-2-methoxybenzyl]-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-3-[2-methoxy-5-(5-oxazolyl)benzyl]amino-2-phenylpiperidine;

(*2S,3S*)-(6-methoxy-2-phenyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)-amine;

(*2S,3S*)-(6-methoxy-2-cyclopropyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(6-methoxy-2-tert-butyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(6-isopropoxyoxy-2-phenyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(6-isopropoxyoxy-2-methyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(6-trifluoromethoxy-2-methyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(6-methoxy-2-methyl-benzoxazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*1SR-2SR,3SR,4RS*)-3-(6-methoxy-3-methylbenzisoxazol-5-yl]methylamino-2-benzhydrylazanorbornane;

(*2S,3S*)-(2-methoxy-5-pyridin-2-ylbenzyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-pyrimidin-2-ylbenzyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-pyridin-3-ylbenzyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-(6-methylpyridin-2-yl)benzyl]-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-[5-(3,5-dimethylpyrazol-1-yl)-2-methoxybenzyl]-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-[2-methoxy-5-(3,4,5-trimethylpyrazol-1-yl)benzyl]-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(2-isopropoxy-5-(3,4,5-trimethylpyrazol-1-yl)benzyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-[5-(3,5-diisopropylpyrazol-1-yl)–2-methoxybenzyl]-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-[5-(3,5-dimethylthiophen-2-yl)–2-methoxybenzyl]-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(6-methoxy-2,3-dimethyl-benzo[b]thiophen-7-ylmethyl)-(2-phenylpiperidin-3-yl)amine.

(*2S,3S*)-(6-methoxy-3-methyl-benzo(d]isoxazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)-amine;

(*1SR,2SR,3SR,4RS*)-(2-benzhydryl-1-aza-bicyclo[2.2.1)hept-3-yl)-6-methoxy-2-methyl-benzothiazol-5-ylmethyl)-amine;

(*2S,3S*)-(6-methoxy-benzoxazol-5-ylmethyl)-(2-phenyl-piperidin-3-yl)-amine;

(*2S,3S*)-(6-methoxy-benzothiazol-5-ylmethyl)-(2-phenyl-piperidin-3-yl)-amine;

(*2S,3S*)-5-methoxy-1-methyl-6-(2-phenylpiperidin-3-ylaminomethyl)-1,3-dihydro-indol-2-one;

(*2S,3S*)-6-methoxy-3-methyl-5-(2-phenylpiperidin-3-ylaminomethyl)-3H-benzoxazo1-2-one;

(*2S,3S*)-6-methoxy-3-methyl-5-(2-phenylpiperidin-3-ylaminomethyl)-3H-benzothiazol-2-one;

(*2S,3S*)-5-methoxy-1,3-dimethyl-6-(2-phenylpiperidin-3-ylaminomethyl)-1,3-dihydro-benzoimidazol-2-one;

(*2S,3S*)-(6-methoxy-3-methyl-3H-benzotriazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-[1,2,3]thiadiazol-4-yl-benzyl)-(2-phenyl-1-azabicyclo[2.2.2]oct-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-[1,2,3]thiadiazol-4-yl-benzyl)-(2-benzhydryl-1-azabicyclo-[2.2.2)oct-3-yl)amine;

(*2S,3S*)-(6-methoxy-2-methyl-benzothiazol-5-ylmethyl)-(2-phenyl-1-azabicyclo-[2.2.2]oct-3-yl)amine;

(*2S,3S*)-(6-methoxy-2-methyl-benzothiazol-5-ylmethyl)-(2-benzhydryl-1-azabicyclo-[2.2.2)oct-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-thiazol-2-yl-benzyl)-(2-benzhydryl-1-azabicyclo(2.2.2)oct-3-yl)amine;

(*2S,3S*)-(6-methoxy-2-methyl-benzothiazol-5-ylmethyl)-(2-phenyl-1-azabicyclo-[2.2.1]hept-3-yl)amine;

(*2S,3S*)-(6-methoxy-2-methyl-benzothiazol-5-ylmethyl)-(2-benzhydryl-l-azabicyclo-[2.2.1]hept-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-[1,2,4]triazol-4-yl-benzyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-(1,2,4)triazol-1-yl-benzyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-thiazol-2-ylbenzyl)-(2-phenyl-decahydroquinolin-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-thiazol-2-ylbenzyl)-(2-phenyl-octahydro-indol-3-yl)amine;

(*2S,3S*)-(2-methoxy-5-oxazol-4-ylbenzyl)-(2-phenylpiperidin-3-yl)amine;

(*2S,3S*)-(6-methoxy-2-(2-propyl)-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)-amine;

(*2S,3S*)-N-[(5-oxo-1H,4H-1,2,4-triazolo)methyl]-2-(4-fluorophenyl)-3-(3,5-ditrifluoromethyl)benzyloxymorpholine;

(*1SR,2SR,3SR,4RS*)-(2-benzhydryl-1-azabicyclo[2.2.1]hept-3-yl)-(6-methoxy-2-phenylbenzothiazol-5-ylmethyl)amine;

(*1SR,2SR,3SR,4RS*)-(2-benzhydryl-1-azabicyclo[2.2.1]hept-3-yl)-(6-methoxy-2-cyclopropylbenzothiazol-5-ylmethyl)amine;

(*1SR,2SR,3SR,4RS*)-(2-benzhydryl-1-azabicyclo[2.2.1]hept-3-yl)-(6-methoxy-2-tert-butylbenzothiazol-5-ylmethyl)amine;

(*1SR,2SR,3SR,4RS*)-(2-benzhydryl-1-azabicyclo[2.2.1)hept-3-yl)-(6-methoxy-2-(2-propyl)benzothiazol-5-ylmethyl)amine;

(*1SR,2SR,3SR,4RS*)-(2-benzhydryi-1-azabicyclo[2.2.1]hept-3-yl)-(6-isopropoxyoxy-2--phenyl-benzothiazol-5-ylmethyl)amine;

(*1SR,2SR,3SR,4RS*)-(2-benzhydryl-1-azabicyclo[2.2.1]hept-3-yl)-(6-isopropoxyoxy-methyl-benzothiazol-5-ylmethyl)amine;

(*1SR,2SR,-3SR,4RS*)-(2-benzhydryl-1-azabicyclo[2.2.1]hept-3-yl)-(6-trifluoromethoxy-2-methyl-benzothiazol-5-ylmethyl)amine;

(6-methoxy-1-oxa-2,3-diazainden-5-ylmethyl)-(2-phenyl-piperidin-3-yl)amine; and

(6-methoxy-2-methyl-1H-benzoimidazol-5-ylmethyl)-(2-phenylpiperidine-3-yl)amine.

(±)-[3R-[3α, 6α (R*)]]-3-phenyl-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxy-5-trifluoromethoxy-phenyl)-7-phenyl-1,8-diazaspiro-[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(5-chloro-2-methoxyphenyl)-7-phenyl-1,8-diazaspiro-[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(5-isopropyl-2-methoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]-undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(5-tert.butyl-2-methoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]-undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxy-5-(N-methyl-N-methylsulfonylaminophenyl)-7-phenyl-1,8-diazaspiro[5.5]-undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-iodophenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxy-4-methylphenyl)-7-phenyl-1,8-diazaspiro[5.5]-undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-isopropoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]-undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-difluoromethoxy-5-trifluoromethoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 5α (R*)]]-3-(2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane;

(±)-[3R-[3α, 5α (R*)]]-3-(2-methoxy-5-trifluoromethoxyphenyl)-6-phenyl-1,7-diazaspiro-[4.5]decane;

(±)-[3R-[3α, 5α (R*)]]-3-(5-chloro-2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane;

(±)-[3R-[3α, 5α (R*)]]-3-(5-isopropyl-2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane;

(±)-[3R-[3α, 5α (R*)]]-3-(5-tert.butyl-2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane;

(*2S, 3S*)-3-(2-Fluoro-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine;

(*2S, 3S*)-3-(2-Chloro-5-(trifluoromethyl)benzyl)amino-2-phenylpipendine;

(*2S, 3S*)-3-(2-Methoxy-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine;

(*2S, 3S*)-3-(2-Phenoxy-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine;

(*2S, 3S*)-3-(5-(1,1-Difluoroethyl)-2-(trifluoromethoxy)benzyl)amino-2-phenylpiperidine;

(*2S,3S*)-3-(5-(1,1-Difluoroethyl)-2-methoxybenzyl)amino-2-phenylpiperidine;

(*2S,3S*)-3-(2-Methoxy-5-(2,2,2-trifluoroethyl)benzyl)amino-2-phenylpiperidine;

(*2S, 3S*)-3-(2-Methoxy-5-(1-(trifluoromethyl)ethyl)benzyl)amino-2-phenylpiperidine;

(*2S,,3S*)-3-[5-(1,1-dimethyl-4,4,4-trifluoro-2-butynyl)-2-methoxybenzyl)amino-2-phenyl piperidine;

(*2S,3S*)-3-[5-(1,1-Dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzylamino]-2-phenylpiperi dine;

(*2S,3S*)-3-(2,4-Dimethoxy-5-(2,2,2-trifluoroethyl)benzyl)amino-2-phenylpiperidine;

(*2S,3S*)-3-[5-[(1-Chloro-1-(trifluoromethyl)ethyl]-2-methoxybenzylamino]-2-phenylpiperidine;

(*2S,3S*)-2-Phenyl-3-(5-(2,2,2-trifluoro-1-(trifluoromethyl)ethyl)-2-methoxybenzyl)amino piperidine;

(*2S,3S*)-2-Phenyl-3-(5-(2,2,2-trifluoro-1-(trifluoromethyl)ethyl)-2-methoxybenzyl)amino piperidine;

(*2S,3S*)-2-Phenyl-3-(5-(1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl)-2-methoxybenzyl)aminopiperidine;

(*2S, 3S*)-3-(2-Methoxy-5-(1,1,2,2,2-pentafluoroethyl)benzyl)amino-2-phenylpiperidine;

(*2S,3S*)-2-Phenyl-3-(5-(2,2,2-trifluoro-1-methyl-1-(trifluoromethyl)ethyl)-2-methoxy-benzyl)aminopiperidine;

(*2S,3S*)-3-[5-[2,2-Difluoro-1-(trifluoromethyl)ethenyl]-2-methoxybenzyl]amino-2-phenyl piperidine;

(*2S,3S*)-3-(2-Methoxy-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)benzyl)-amino-2-pheriylpiperidine;

(*2S, 3S*)-3-[5-Methoxy-1-(trifluoromethyl)indan-6-yl)methylamino]-2-phenylpiperidine;

(*2S,3S*)-3-((6-Methoxy-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-7-yl)methyl)amino-2-phenylpiperidine;

(*2S,3S*)-3-((2,2-Difluoro-6-methoxy-1,2,3,4-tetrahydronaphthalen-7-yl)methyl)amino-2-phenylpiperidine;

(*2S,3S*)-3-(6-methoxy-1,3,3-trimethyloxindol-5-yl)methylamino-2-phenylpiperidine;

(2S,3S)-3-(6-methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylamino-2-phenylpiperidine;

(2S,3S)-3-(6-isopropoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylamino-2-phenylpiperidine;

(2S,3S)-3-(1-isopropyl-6-methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylamino-2-phenylpiperidine;

(2S,3S)-3-[(6-methoxy-1-methyl-2-thioxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino-2-phenylpiperidine dihydrochloride;

(2S,3S)-3-[(7-methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino-2-phenylpiperidine dihydrochloride;

(2S,3S)-3-[(6-methoxy-1-methyl-2-oxo-4H-3,1-benzothiazin-7-yl)methyl]amino-2-phenylpiperidine dihydrochloride.

(2S,3S)-3-[(6-methoxy-1-methyl-2-oxo-4H-3,1-benzothiazin-7-yl)methyl]amino-2-phenylpiperidine dihydrochloride;

(2S, 3S, 4R)-2-diphenylmethyl-3-[(2-methoxy-4,5-dimethylphenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-4,5-dimethylphenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(methylethyl)phenyl)methylamino]-4-(carbomethoxymethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(methylethyl)phenyl)methylamino]-4-(carboxymethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(methylethyl)phenyl)methylamino]-4-(2-dimethylamino-carbamoylethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-trifluoromethoxyphenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2S, 3S, 4R)-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-methoxyethyl)- pyrrolidine;

(2S, 3S, 4R)-2-diphenylmethyl-3-[(2-methoxy-5-methylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-methylethyl)phenyl)methylamino]-4-(2-methoxyethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methyl-5-(1,1-dimethylethyl)phenyl)methyl-amino]-4-(2-hydroxyethyl)- pyrrolidine;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-4,5-dimethylphenyl)-methylamino]-bicyclo[2.2.1]- heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxyphenyl)methyl-amino]bicyclo[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)-phenyl)methylamino]bicyclo- [2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-trifluoromethoxy-phenyl)methylamino]bicyclo- [2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1-methylethyl)phenyl)-methylamino]bicyclo- [2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-propylphenyl)methyl-amino]bicyclo[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1-methylpropyl)-phenyl)methylamino]bicyclo- [2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-phenyl-3-[(2-methoxyphenyl)methyl-amino]bicyclo[2.2.1]heptane;

(1SR, 2SR, 3RS, 4RS)-1-aza-2-phenyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methyl-amino]bicyclo[2.2.1]heptane;

(2SR, 3SR, 4RS)-N-1-phenylmethyl-2-diphenylmethyl-3-[(2-methoxyphenyl)methyl-amino]-4-(2-hydroxyethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-phenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methyl-amino]-4-(2-hydroxyethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methyl-amino]-4-(2-hydroxyethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1-methylethyl)phenyl)methyl-amino]-4-(2-hydroxyethyl)- pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-propylphenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1-methyl-1-propyl)phenyl)methyl-amino]-4-(2-hydroxy-ethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-trifluoromethoxy-5-(1,1-dimethylethyl)-phenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-chlorophenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-phenyl-3-[(2-methoxyphenyl)methyl-amino]-4-(2-hydroxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-phenyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-hydroxy-ethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-phenyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]-4-(2-hydroxy-ethyl)pyrrolidine;

6-Methoxy-1,3,3-trimethyl-5-[(2-phenyl-piperidin-3-ylamino)-methyl]-3-dihydro-indol-2-one;

6-Methoxy-1,methyl-7-[(2-phenyl-piperidin-3-ylamino)-methyl]-,3-4-dihydro-1H-quindol-2-one;

6-Methoxy-1,2-dimethyl-1,2,3,4-terrahydro-quinolin-7-ylmethyl)-(2-phenyl-piperidin-3-yl)-amine;

6-Isopopoxy-1-methyl-7-[(2-phenyl-piperidin-3-ylamino)-methyl]-3,4-dihydro-1H-quinolin-2-one;

7-Methoxy-1-methyl-6-[(2-phenyl-piperidin-3-ylamino)-methyl]-3,4-dihydro-1H-quinolin-2-one;

6-Methoxy-1-methyl-7-[(2-phenyl-piperidin-3-ylamino)-methyl]-1,4-dihydro-benzo-[d][1,3]thiazin-2-one;

6-Methoxy-7-[(2-phenyl-piperidin-3-ylamino)-methyl]1-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-quinolin-2-one;

6-Isopopoxy-1-methyl-7-[(2-phenyl-piperidin-3-ylamino)-methyl]-3,4-dihydro-1H-quinolin-2-thione; and

6-Methoxy-1,3-dimethyl-7-[(2-phenyl-piperidin-3-ylamino)-methyl]-3,3-dihydro-1H-quinolin-2-one.

Preferred embodiments of this invention relate to the above pharmaceutical compositions for the treatment of anxiety or depression, and the above methods of treating anxiety or depression, wherein the NK-1 receptor antagonist, or pharmaceutically acceptable salt thereof, is selected from the following compounds and their pharmaceutically acceptable salts:

(6-Methoxy-3-trifluoromethyl-benzo[d]isoxazol-5-ylmethyl)-(2-phenyl-piperidin-3-yl)-amine;

6-Methoxy-1-methyl-7-[(2-phenyl-1-propyl-piperidin-3-ylamino)-methyl]-3,4-dihydro-1H-quinolin-2-one;

6-Methoxy-1-methyl-7-{[1-(5-oxo-2,5-dihydro-1H-[1,2,4]triazol-3-ylmethyl)-2-phenyl-piperidin-3-ylamino]-methyl}-3,4-dihydro-1H-quinolin-2-one;

3-(2-Methoxy-5-trifluoromethoxy-phenyl)-6-phenyl-1,7-diaza-spiro[4.5]decane;

6-Methoxy-1-methyl-7-[(2-phenyl-piperidin-3-ylamino)-methyl]-3,4-dihydro-1H-quinolin-2-one;

[2-Methoxy-5-(2,2,2-trifluoro-1-trifluoromethyl-ethyl)-benzyl]-(2-phenyl-piperidin-3-yl)-amine;

(*2S,3S*)-N-[(5-oxo-1H,4H-1,2,4-triazolo)methyl]-2-(4-fluorophenyl)-3-(3,5-ditrifluoromethyl)benzyloxymorpholine;

[5-(1,1-Dimethyl-prop-2-ynyl)-2-methoxy-benzyl]-(2-phenyl-piperidin-3-yl)-amine;

7-Methoxy-1-methyl-6-[(2-phenyl-piperidin-3-ylamino)-methyl]-3,4-dihydro-1H-quinolin-2-one;

[2-Methoxy-5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-benzyl]-(2-phenyl-piperidin-3-yl)-amine;

(7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethyl)-(2-phenyl-piperidin-3-yl)-amine;

[2-Methoxy-5-(1-methyl-1-trifluoromethyl-prop-2-ynyl)-benzyl]-(2-phenyl-piperidin-3-yl)-amine;

(6-Methoxy-1-methyl-1-trifluoromethyl-isochroman-7-ylmethyl)-(2-phenyl-piperidin-3-yl)-amine;

2-{3-[(2-Benzhydryl-1-aza-bicyclo[2.2.2]oct-3-ylamino)-methyl]-4- methoxy-phenyl}-2-methyl-propan-1-ol;

3-(3,5-Bis-trifluoromethyl-benzyloxy)-2-phenyl-piperidine;

5-[2-(3,5-Bis-trifluoromethyl-benzyloxy)-3-phenyl-morpholin-4-ylmethyl]-2,4-dihydro-[1,2,4]triazol-3-one;

(2S, 3S)-3-(2-Methoxy-5-(trifluoromethoxy)benzyl)amino-2-phenylpiperidine;

(2S, 3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]-octan-3-amine;

(2S,3S)-N-[(5-oxo-1H,4H-1,2,4-triazolo)methyl]-2-(4-fluorophenyl)-3-(3,5-ditrifluoromethyl)benzyloxymorpholine;

(2S, 3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]-octane-3-amine;

(2S, 3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]-octan-3-amine; and

(2S,3S)-N-(5-n-propyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]-octane-3-amine.

The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined as above.

The term "one or more substituents", as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

The terms “anxiolytic effective amount” and “antianxiety effective amount”, as used herein, refer to an amount that is effective in treating anxiety.

The term “antidepressant effective amount”, as used herein, refers to an amount that is effective in treating depression.

The term “treating” refers to, and includes, reversing, alleviating, inhibiting the progress of, or preventing a disease, disorder or condition, or one or more symptoms thereof; and “treatment” and “therapeutically” refer to the act of treating, as defined above.

The pharmaceutical compositions and methods of this invention comprise, or comprise administering NK-1 receptor antagonists of the formulas I through XXI, which may have chiral centers and therefore exist in different enantiomeric forms. This invention includes methods and pharmaceutical compositions, as described above, wherein the NK-1 receptor antagonists that are employed are optical isomers, tautomers or stereoisomers of the compounds of formulas I through XXI that are defined above, or mixtures thereof.

This present invention also relates to pharmaceutical compositions and methods comprising, or comprising administering, pharmaceutically acceptable acid addition salts of NK-1 receptor antagonists and of antidepressant and anxiolytic agents. The possible acids which are used to prepare the pharmaceutically acceptable acid addition salts of the basic active agents employed in the methods and pharmaceutical compositions of this invention are those which form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3- naphthoate)]salts.

This invention also relates to pharmaceutical compositions and methods comprising, or comprising administering, pharmaceutically acceptable base addition salts of NK-1 receptor antagonists and of antidepressant and anxiolytic agents. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of the acidic active agents that are employed in the methods of this invention are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (*e.g.*, potassium and sodium) and alkaline earth metal cations (*e.g.*, calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine (meglumine), and the lower alkanol ammonium and other base salts of pharmaceutically acceptable organic amines.

The subject invention also relates to pharmaceutical compositions and methods of treatment that employ isotopically-labeled compounds that are identical to those recited in formulas I through XXI, or to other NK-1 receptor antagonists, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the NK-1 receptor antagonists that are employed in the pharmaceutical compositions and methods of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. The NK-1 receptor antagonists employed in the pharmaceutical compositions and methods of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes are within the scope of this invention. Certain isotopically-labeled NK-1 receptor antagonists, for example, those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^{3}H, and carbon-14, *i.e.*, ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, *i.e.*, ^{2}H, can afford certain therapeutic advantages resulting from

greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

Detailed Description of the Invention

The following references refer, collectively, to quinuclidine, piperidine, ethylene diamine, pyrrolidine and azanorbornane derivatives and related compounds that exhibit activity as NK-1 receptor antagonists and that can be used, in combination with eletripan, in the pharmaceutical compositions and methods of this invention, and to methods of preparing the same: United States Patent 5,162,339, which issued on November 11, 1992; United States Patent 5,232,929, which issued on August 3, 1993; World Patent Application WO 92/20676, published November 26, 1992; World Patent Application WO 93/00331, published January 7, 1993; World Patent Application WO 92/21677, published December 10, 1992; World Patent Application WO 93/00330, published January 7, 1993; World Patent Application WO 93/06099, published April 1, 1993; World Patent Application WO 93/10073, published May 27, 1993; World Patent Application WO 92/06079, published April 16, 1992; World Patent Application WO 92/12151, published July 23, 1992; World Patent Application WO 92/15585, published September 17, 1992; World Patent Application WO 93/10073, published May 27, 1993; World Patent Application WO 93/19064, published September 30, 1993; World Patent Application WO 94/08997, published April 28, 1994; World Patent Application WO 94/04496, published March 3, 1994; World Patent Application WO 95/07908, published March 3, 1995; World Patent Application WO 94/20500, published September 15, 1994; World Patent Application WO 94/13663, published June 23, 1994; World Patent Application WO 95/16679, published June 22, 1995; World Patent Application WO 97/08144, published March 6, 1997; World Patent Application WO 97/03066, published January 30, 1997; World Patent Application WO 99/25714, published May 27, 1999; United States Patent Application 988,653, filed December 10, 1992; United States Patent Application 026,382, filed March 4, 1993; United States Patent Application 123,306, filed September 17, 1993, and United States Patent Application 072,629, filed June 4, 1993. All of the foregoing World Patent Applications designate the United States. The foregoing patents and patent applications are incorporated herein by reference in their entirety.

NK-1 receptor antagonists of the formula I can be prepared as described in the following patents and patent applications, all of which are referred to above and incorporated herein by reference in their entirety: WO 93/00331, WO 92/21677, WO 92/15585, WO 92/01688, WO 93/06099, WO 91/18899, United States Patent 5,162,339,and United States Patent 5,232,929. NK-1 receptor antagonists of the formula Ia (*i.e.*, compounds defined identically to compounds of the formula I, but having the further proviso that when neither X^1, X^2 nor X^3 is a fluorinated alkoxy group, at least one of R^1, R^3, R^4, R^5, R^6, R^7 and R^{13} is an aryl group substituted with a fluorinated alkoxy group) can be prepared as described in WO 93/00331.

NK-1 receptor antagonists of the formula IXa and IXb can be prepared as described in World Patent Application WO 94/13663, published June 23, 1994.

NK-1 receptor antagonists of the formula XVIII can be prepared as described in World Patent Application WO 97/08144, published March 6, 1997.

NK-1 receptor antagonists of the formula XIX can be prepared as described in World Patent Application WO 97/03066, published January 30, 1997 and World Patent Application WO 99/25714, published May 27, 1999.

NK-1 receptor antagonists of the formula XX can be prepared as described in World Patent Application WO 94/20500, published September 15, 1994.

NK-1 receptor antagonists of the formula XXI can be prepared as described in World Patent Application WO 93/00330, published January 7, 1993.

Other NK-1 receptor antagonists that can be used, together with an anxiolytic or antidepressant agent in the pharmaceutical compositions and methods of this invention are those compounds and pharmaceutically acceptable salts described in the following references: European Patent Application EP 499,313, published August 19, 1992; European Patent Application EP 520,555, published December 30, 1992; European Patent Application EP 522,808, published January 13, 1993, European Patent Application EP 528,495, published February 24, 1993, PCT Patent Application WO 93/14084, published July 22, 1993, PCT Patent Application WO 93/01169, published January 21, 1993, PCT Patent Application WO 93/01165, published January 21, 1993, PCT Patent Application WO 93/01159, published January 21, 1993, PCT Patent Application WO 92/20661, published November 26, 1992, European Patent Application EP 517,589, published December 12, 1992, European Patent Application EP 428,434, published May 22, 1991, European Patent Application EP 360,390, published March 28, 1990; and United States Provisional Patent Applications Serial No. 60/195,922, filed April 10, 2000, and Serial No. 60/212,922, filed June 20, 2000. All of the foregoing World Patent Applications designate the United States. The foregoing patents and patent applications are incorporated herein by reference in their entirety.

This invention relates both to methods of treating anxiety or depression in which the NK-1 receptor antagonist and the anxiolytic or antidepressant agent, or pharmaceutically acceptable salts of the same, are administered together, as part of the same pharmaceutical composition, as well as to methods in which these two active agents are administered separately as part of an appropriate dose regimen designed to obtain the benefits of the combination therapy. The appropriate dose regimen, the amount of each dose administered, and specific intervals between doses of each active agent will depend upon the subject being treated, the emetogen and the severity of the condition. Generally, in carrying out the methods of this invention, the NK-1 receptor antagonist will be administered to an adult human in an amount ranging from about 0.05 to about 1500 mg per day, in single or divided doses, preferably from about 5 to about 200 mg/day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily. A suitable dosage level for the antidepressant agent is about 0.5 to 1500 mg per day, preferably about 2.5

to 1000 mg per day, and especially about 2.5 to 500 mg per day. The compounds may be administered on a regimen of up to 6 time per day, preferably 1 to 4 times per day, especially 2 time per day and most especially once daily. A suitable dosage level for the anxiolytic agent is about 0.5 to 1500 mg per day, preferably about 2.5 to 1000 mg per day, and especially about 2.5 to 500 mg per day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The NK-1 receptor antagonists, their pharmaceutically acceptable salts, and the antidepressant and anxiolytic agents and their pharmaceutically acceptable salts that are employed in the pharmaceutical compositions and methods of this invention are hereinafter also referred to as "therapeutic agents". The therapeutic agents can be administered via either the oral or parenteral route. Compositions containing both an NK-1 receptor antagonist and an anxiolytic or antidepressant agent, or pharmaceutically acceptable salts of one or both therapeutic agents, will generally be administered orally or parenterally daily, in single or divided doses, so that the total amount of each active agent administered falls within the above guidelines.

The therapeutic agents may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the therapeutic agents of this invention can be administered in a wide variety of different dosage forms, *i.e.*, they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, suppositories, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, *etc.* Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutic agents of this invention, when administered separately (*i.e.*, not in the same pharmaceutical composition) are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like

polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic agent in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

As stated above, the NK-1 receptor antagonist and the anxiolytic or antidepressant agent may be formulated in a single pharmaceutical composition or alternatively in individual pharmaceutical compositions for simultaneous, separate or sequential use in accordance with the present invention.

Preferably the compositions according to the present invention, which contain both an NK-1 receptor antagonist and an anxiolytic agent or an antidepressant, as well as the pharmaceutical compositions used to deliver only one of these active agents, are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, by inhalation or insufflation or administration by transdermal patches or by buccal cavity absorption wafers.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing, typically, from 0.05 to about 500 mg of each of the therapeutic agents contained in the composition. The tablets or pills of the composition can be coated or otherwise compounded

to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac acetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethyl cellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration of an NK-1 receptor antagonist or other therapeutic agent by injection include those comprising the therapeutic agent in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (*e.g.*, Tween™ 20, 40, 60, 80 or 85) and other sorbitans (*e.g.*, Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn ™, Infonutrol™ , Lipofundin ™ and Lipiphysan™. The therapeutic agent may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (*e.g.*, soybean oil, safflower oil, cottonseed oil, sesame oil, com oil or almond oil) and an emulsion formed upon mixing with a phospholipid (*e.g.*, eggs phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0 μm, particularly 0.1 and 0.5 μm, and have a pH in the range of 5.5 to 8.0.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents or mixtures thereof, and powders.

The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising devise may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

Compositions of the present invention may also be presented for administration in the form of transdermal patches using conventional technology. The compositions may also be administered via the buccal cavity using, for example, absorption wafers.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising an NK-1 receptor antagonist and an antidepressant or anxiolytic agent, or pharmaceutically acceptable salts of the same, which process comprises bringing an NK-1 receptor antagonist and the antidepressant or anxiolytic agent (or the pharmaceutically acceptable salts of one or both of these therapeutic agents) into association with a pharmaceutically acceptable carrier or excipient.

It will be appreciated that the amount of the NK-1 receptor antagonist and the antidepressant or anxiolytic agent required for use in the treatment of depression or anxiety will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the patient's physician or pharmacist.

The activity of the compounds of the present invention, as substance P antagonists, is determined by their ability to inhibit the binding of substance P at its receptor sites in CHO-cells which reveal NK-1 receptor or IM–9 cells employing radioactive ligands. The substance P antagonist activity of the herein described piperidine compounds is evaluated using the standard assay procedure described by M. A. Cascieri *et al.*, as reported in The Journal of Immunology, 133, 3260 (1984). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues or IM-9 cells, thereby affording characteristic IC_{50} values for each compound tested. More specifically, inhibition of [^{3}H]SP binding to human IM-9 cells by compounds is determined in assay buffer (50 mM Tris-HCl (ph 7.4), 1mM $MnCl_2$, 0.02% bovine serum albumin, bacitracin (40 μg/ml) leupeptin (4 μg/ml), chymostatin (2 μg/ml) and phosphoramidon (30 μg/ml). The reaction is initiated by the addition of cells to the assay buffer containing 0.56 nM [^{3}H]SP and various concentrations of compounds (total volume; 0.5 ml) and allowed to incubate for 120 minutes at 4°C. Incubation is terminated by filtration onto GF/B filters (presoaked in 0.1%

polyethylenimine for 2 hours). Nonspecific binding is defined as the radioactivity remaining in the presence of 1μM SP. The filters are placed into tubes and counted using a liquid scintillation counter.

When administered in combination, either as a single or as separate pharmaceutical composition(s), the CNS-penetrant NK-1 receptor antagonist and an antidepressant or anti-anxiety agent, are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anxiolytic agent will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to I and 100 to 1.

As used herein the term "patient" includes animals of economic importance such as bovine, ovine, and porcine animals, especially those that produce meat, as well as domestic animals (*e.g.* cats and dogs), sports animals (*e.g.* horses), zoo animals, and humans, the latter being preferred.

As used herein, the term "CNS-penetrant" refers to NK-1 receptor antagonists which are able to inhibit NK-1 receptor agonist-induced foot-tapping in the gerbil as hereinafter defined.

Essentially, hind foot-tapping in the gerbil induced by infusion of the NK-1 receptor agonist, GR73632 (d Ala[L-Pro^9,Me-Leu^{10}] -substance P(7-1 1)), under anaesthesia, directly into the central ventricles is inhibited when a CNS-penetrant NK-I receptor antagonist is administered intravenously immediately prior to GR73632 challenge, wherein hind foot-tapping over a period of five minutes following recovery from the anaesthesia is inhibited with an ID_{50}≤3mg/kg, and preferably with an ID_{50}≤1mg/kg.

In an alternative method, the NK-1 receptor antagonist is administered orally, I hour prior to GR73632 challenge, wherein the foot-tapping over a period of five minutes following recovery from anaesthesia is inhibited with an ID_{50}≤30mg/kg, and preferably with an ID_{50}≤10mg/kg.

CNS-penetrant NK-1 receptor antagonists of use in the present invention are also effective in the attenuation of separation-induced vocalizations by guinea-pig pups as hereinafter defined.

Essentially, a vocalization response in guinea-pig pups is induced by isolation from their mothers and littermates, which response is attenuated when a CNS-penetrant NK- I receptor antagonist is administered subcutaneously 30 minutes prior to isolation, wherein vocalizations during the first 15 minutes of isolation are attenuated with an ID_{50}≤20mg/kg, preferably with an ID_{50}≤10mg/kg, and especially with an ID_{50}≤5mg/kg.

In an alternative method, the NK-1 receptor antagonist is administered orally, 4 hours prior to isolation, wherein vocalizations during the first 15 minutes of isolation are attenuated with an ID_{50} ≤20mg/kg, preferably with an ID_{50} ≤10mg/kg, and especially with an ID_{50} ≤5mg/kg.

The following examples illustrate pharmaceutical compositions according to the invention. The formulations may be prepared with separate active ingredients or with a combination of active ingredients in one composition. In such combined preparations, the ration of the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anti-anxiety agent will depend upon the choice of active ingredients.

EXAMPLE 1

Tablets Containing 50-300 mg of NK-1 Antagonist and 50-100 mg of Sertraline

	Amount mg					
NK-1 antagonist	20.0	20.0	100.0	100.0	300.0	300.0
Sertraline	50.0	100.0	50.0	100.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0	80.0	80.0	80.0
Lactose	184.5	179.5	134.5	129.5	134.5	129.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5

	Amount mg					
NK-1 antagonist	5.0	15.0	50.0	5.0	15.0	50.0
Sertraline	50.0	50.0	50.0	100.0	100.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0	80.0	80.0	80.0
Lactose	184.5	179.5	134.5	129.5	134.5	129.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5

EXAMPLE 2

Tablets Containing 50-300 mg of NK-1 Antagonist and 50-100 mg of Ziprasidone

	Amount mg								
NK-1 antagonist	20.0	20.0	20.0	100.0	100.0	100.0	300.0	300.0	300.0
Ziprasidone	40.0	80.0	160.0	40.0	80.0	160.0	40.0	80.0	160.0
Microcrystalline cellulose	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Lactose	184.5	179.5	134.5	129.5	134.5	129.5	129.5	129.5	129.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

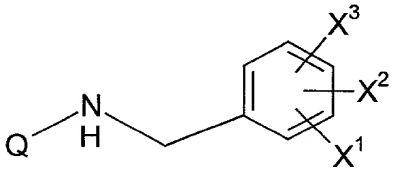
	Amount mg								
NK-1 antagonist	5.0	15.0	50.0	5.0	15.0	50.0	5.0	15.0	50.0
Ziprasidone	40.0	80.0	160.0	80.0	160.0	40.0	160.0	40.0	80.0
Microcrystalline cellulose	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Lactose	184.5	179.5	134.5	129.5	134.5	129.5	129.5	129.5	129.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

The active ingredients cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate.

CLAIMS

1. A pharmaceutical composition for the treatment of anxiety or depression in a mammal, comprising: (a) a compound that exhibits activity, respectively, as an anxiolytic agent or an antidepressant, or a pharmaceutically acceptable salt thereof; (b) a CNS-penetrant NK-1 receptor antagonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, anxiety or depression.

2. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula I, as defined below, and their pharmaceutically acceptable salts:

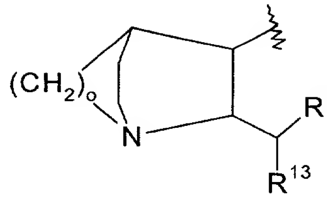


I

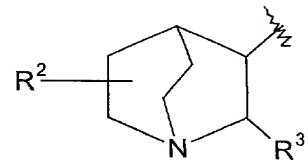
wherein X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6) alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and

Q is a group of the formula



II



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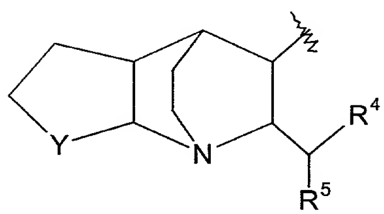

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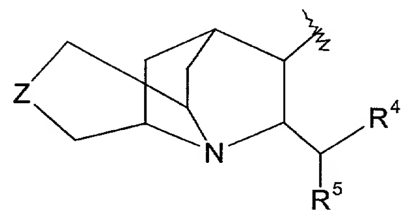

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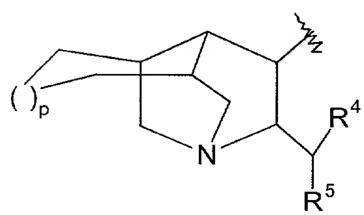
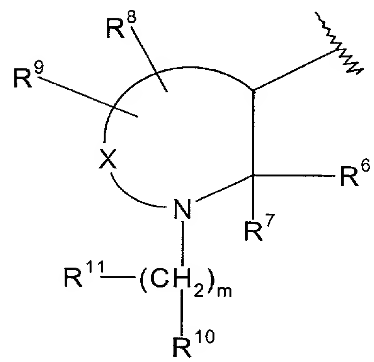
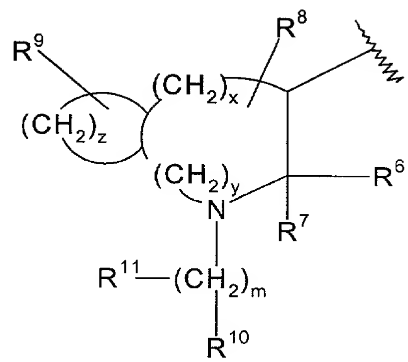


VI



VII

OR



VIII

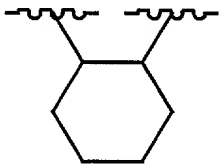
wherein R^1 is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and $(C_1\text{-}C_3)$ alkoxy-carbonyl;

R^{13} is selected from $(C_3\text{-}C_4)$ branched alkyl, $(C_5\text{-}C_6)$ branched alkenyl, $(C_5\text{-}C_7)$ cycloalkyl, and the radicals named in the definition of R^1;

R^2 is hydrogen or $(C_1\text{-}C_6)$ alkyl;

R^3 is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R^3 may optionally be substituted with from one to three substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



(J)

;

Z is oxygen, sulfur, amino, $(C_1\text{-}C_3)$alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

o is two or three;

p is zero or one;

R^4 is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms, carboxy, $(C_1\text{-}C_3)$ alkoxy-carbonyl and benzyloxycarbonyl;

R^5 is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;

X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^8, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^9;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{11};

R^6 is a radical selected from hydrogen, $(C_1\text{-}C_6)$ straight or branched alkyl, $(C_3\text{-}C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl,

furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl,(C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^7 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^6 and R^7, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^8 and R^9 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,-(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^6;

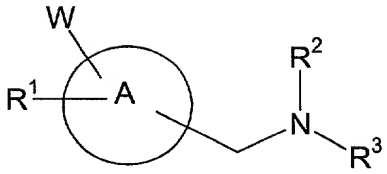
R^{10} is $NHCR^{12}$, $NHCH_2R^{12}$, $NHSO_2R^{12}$ or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9;

R^{11} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9; and

R^{12} is (C_1-C_6)alkyl, hydrogen, phenyl(C_1-C_6)alkyl or phenyl optionally substituted with (C_1-C_6) alkyl; and

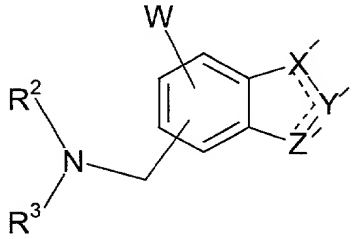
with the proviso that (a) when m is 0, R^{11} is absent, (b) neither R^8, R^9, R^{10} nor R^{11} can form, together with the carbon to which it is attached, a ring with R^7, (c) when Q is a group of the formula VIII, R^8 and R^9 cannot be attached to the same carbon atom, and (d) when R^8 and R^9 are attached to the same carbon atom, then either each of R^8 and R^9 is independently selected from hydrogen, fluoro, (C_1-C_6) alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^8 and R^9, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached.

3. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula IXa or IXb, as defined below, and their pharmaceutically acceptable salts:



IXa

or



IXb

and their pharmaceutically acceptable salts, wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the side chain containing NR^2R^3 is attached to a carbon atom of ring system A;

W is hydrogen, $(C_1$-$C_6)$alkyl optionally substituted with from one to three fluorine atoms, -$S(O)_v$-$(C_1$-$C_6)$ alkyl wherein v is zero, one or two, halo, benzyloxy or $(C_1$-$C_6)$alkoxy optionally substituted with from one to three fluorine atoms;

R^1 is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazolyl or thiophenyl), wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from $(C_1$-$C_6)$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1$-$C_6)$ alkoxy optionally substituted with from one to three fluorine atoms;

the dotted lines in formula Ib indicate that one of the X'-Y' and Y'-Z' bonds may optionally be a double bond;

X' is selected from =CH-, $-CH_2$-, -O-, -S-, -SO-, $-SO_2$-, $-N(R^4)$-, -NH-, =N-, -CH[$(C_1$-$C_6)$alkyl]-, =C[$(C_1$-$C_6)$alkyl]-, $-CH(C_6H_5)$- and $=C(C_6H_5)$-;

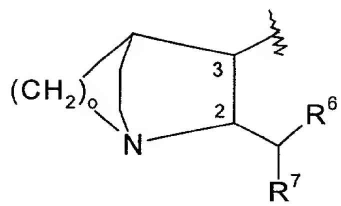
Y' is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2$-, =C[$(C_1$-$C_6)$alkyl]-, -CH[$(C_1$-$C_6)$alkyl]-, $=C(C_6H_5)$-, $-CH(C_6H_5)$-, =N-, -NH-, $-N(R^4)$-, =C(halo)-, $=C(OR^4)$-, $=C(SR^4)$-, $=C(NR^4)$-, -O-, $=C(CF_3)$-, $=C(CH_2C_6H_5)$-, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)$- and -$CH(C_6H_5)$- may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of said =[$(C_1$-$C_6)$alkyl]- and -CH[C_1-$C_6)$alkyl]- may optionally be substituted with from one to three fluorine atoms;

Z' is selected from =CH-, $-CH_2$-, =N-, -NH-, -S-, $-N(R^4)$-, $=C(C_6H_5)$-, $-CH(C_6H_5)$-, =C[$(C_1$-$C_6)$ alkyl]- and -CH[$(C_1$-$C_6)$alkyl]-;

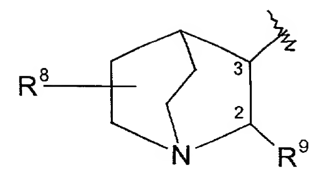
or X', Y' and Z', together with the two carbon atoms shared between the benzo ring and the X'Y'Z' ring, form a fused pyridine or pyrimidine ring;

R^2 is hydrogen or $-CO_2(C_1-C_{10})$alkyl;

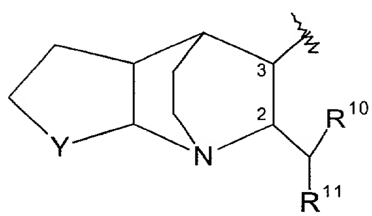
R^3 is selected from



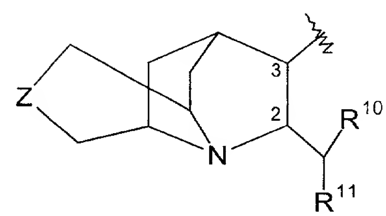
V



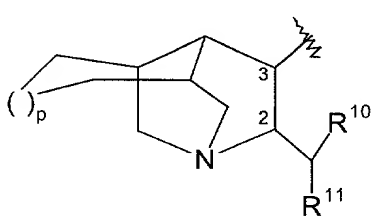
XI



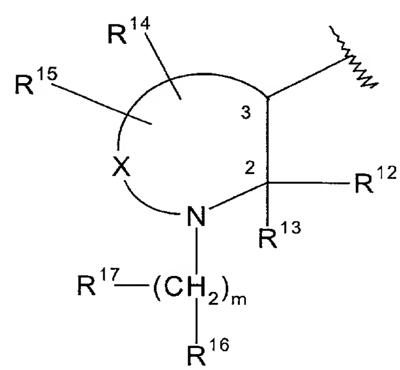
XII



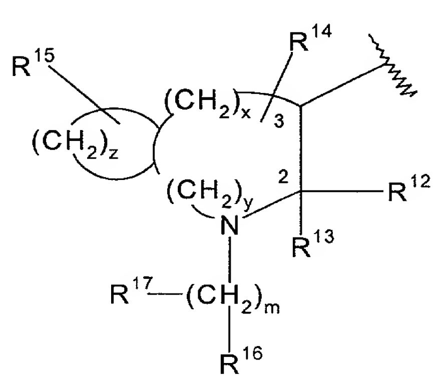
XIII



XIV

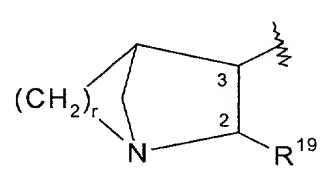


XV



XVI

and



XVII

wherein R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl, wherein said phenyl may optionally be substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and $(C_1\text{-}C_3)$ alkoxy-carbonyl;

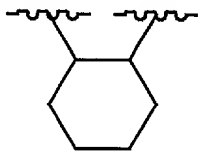
R^4 is $(C_1\text{-}C_6)$ alkyl or phenyl;

R^7 is selected from $(C_3\text{-}C_4)$ branched alkyl, $(C_5\text{-}C_6)$ branched alkenyl, $(C_5\text{-}C_7)$ cycloalkyl, and the radicals named in the definition of R^6;

R^8 is hydrogen or $(C_1\text{-}C_6)$ alkyl;

R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



(J)

;

Z is oxygen, sulfur, amino, $(C_1\text{-}C_3)$alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

x is zero, one or two;

y is zero, one or two;

z is three, four or five;

o is two or three;

p is zero or one;

r is one, two or three;

the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbon atoms of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;

X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};

R^{12} is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6) alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^{13} is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to such point of attachment may optionally be replaced by oxygen, nitrogen or sulfur;

R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C(=O)-OH, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^{12};

R^{16} is $NHC(=O)R^{18}$, $NHCH_2R^{18}$, SO_2R^{18}, CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};

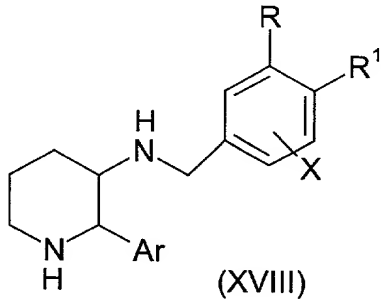
R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and

R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula XVI, R^{14} and R^{15} cannot be attached to the same

carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, $(C_1\text{-}C_6)$alkyl, hydroxy-$(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a $(C_3\text{-}C_6)$ saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} can not both be hydrogen, and (e) when R^{14} or R^{15} is attached to a carbon atom of X or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom.

4. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XVIII, as depicted and defined below, and their pharmaceutically acceptable salts:



(XVIII)

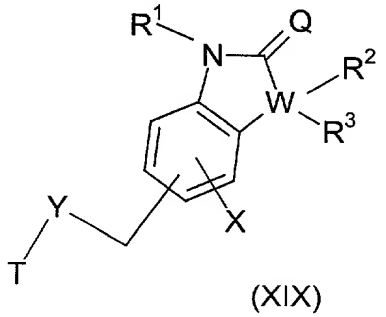
wherein R is halo $(C_1\text{-}C_8)$alkyl, halo $(C_2\text{-}C_8)$alkenyl, halo $(C_2\text{-}C_8)$alkynyl or halo $(C_1\text{-}C_8)$alkyl substituted by hydroxy or $(C_1\text{-}C_8)$alkoxy; R^1 is hydrogen, halo or $(C_1\text{-}C_6)$alkoxy; or

R and R^1, together with the two carbon atoms shared between the benzene ring and the R and R^1, complete a fused $(C_4\text{-}C_6)$cycloalkyl wherein one carbon atom is optionally replaced by oxygen and wherein one or two of the carbon atoms are optionally substituted by up to five subtituents selected from halo, $(C_1\text{-}C_6)$alkyl and halo $(C_1\text{-}C_6)$alkyl;

X is $(C_1\text{-}C_6)$alkoxy, halo $(C_1\text{-}C_6)$alkoxy, phenoxy or halo; and

Ar is phenyl optionally substituents by halo.

5. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XIX, as depicted and defined below, and their pharmaceutically acceptable salts:



(XIX)

wherein

W is methylene, ethylene, propylene, vinylene, $-CH_2-O-$,$-O-CH_2-$, $-CH_2-S-$ or $-S-CH_2-$;

R^1, R^2 and R^3 are independently hydrogen, (C_1-C_3) alkyl, (C_1-C_3) alkoxy or halo (C_1-C_3) alkyl, provided that when W is methylene, both R^2 and R^3 are not hydrogen;

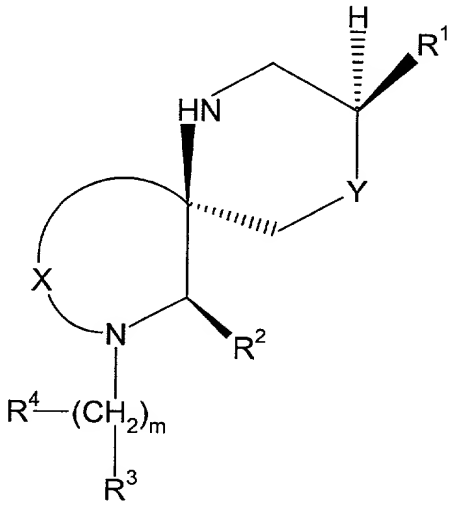
X is halo, (C_1-C_3) alkoxy, (C_1-C_3) alkoxy or (C_1-C_3) alkenyl;

Y is imino or oxy;

Q is oxygen or sulfur; and

T is (2S,3S)-2-diphenylmethylquinuclidin-3-yl,(2S,3S)-2-phenylpiperdin-3-yl or (2S,3S)-2-diphenylmethyl-1-azanorbornan-3-yl.

6. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XX, as depicted and defined below, and their pharmaceutically acceptable salts:

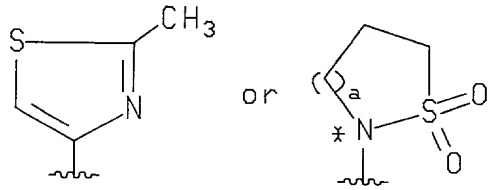


XX

wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, $-C(=O)-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$C(=O)-NH-(C_1-C_6)$ alkyl, hydroxy(C_1-C_4)alkyl,$-NHC(=O)H$, $-NHC(=O)-(C_1-C_6)$ alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-S(O)_v-(C_1-C_{10})$-alkyl wherein v is zero, one or two, $-S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, $-SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, $(SO_2-(C_1-C_{10})$alkyl) $((C_1-C_{10})$alkyl)N wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and $(SO_2$-aryl) $((C_1-C_{10})$alkyl)N; and wherein the aryl moieties of said $-S(O)_v$-aryl, -O-aryl and $(SO_2$-aryl) $((C_1-C_{10})$alkyl)N are independently selected from phenyl and benzyl and may

optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;

or R^1 is phenyl substituted with a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R^1;

R^2 is selected from (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;

R^3 is selected from $NHC(=O)R^8$, $NHCH_2R^8$, SO_2R^8, AR^5, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;

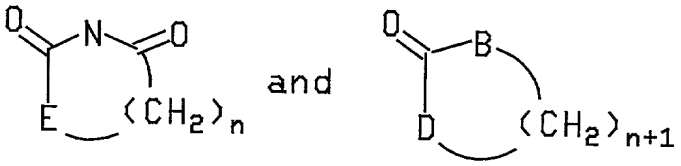
A is CH_2, nitrogen, oxygen, sulfur or carbonyl;

R^8 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

R^4 is selected from oximino (=NOH) and the radicals set forth in the definitions of R^2, R^6 and R^7;

R^5 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl,

thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with $(C_1$-$C_6)$alkyl or $(C_2$-$C_6)$ spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a $(C_3$-$C_5)$ fused carbocyclic ring;

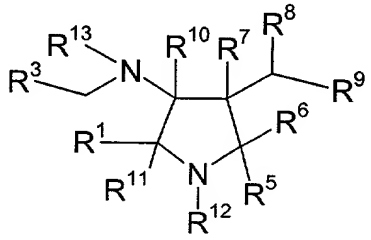
X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;

R^6 and R^7 are independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy, -C(=O)-OH, $(C_1$-$C_6)$alkyl-O-C(=O)-, $(C_1$-$C_6)$alkyl-O-C(=O)-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-C(=O)-O-, $(C_1$-$C_6)$alkyl-C(=O)-$(C_1$-$C_6)$alkyl-O-, $(C_1$-$C_6)$alkyl-C-, $(C_1$-$C_6)$alkyl-C(=O)-$(C_1$-$C_6)$alkyl- and the radicals set forth in the definition of R^2; and

Y is $(CH_2)_z$ wherein z is zero or one;

with the proviso that: (a) when A is -(CH_2)- or carbonyl, R^5 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom;

7. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XXI, as depicted and defined below, and their pharmaceutically acceptable salts:



XXI

wherein R^1 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)- (C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, phenyl, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6) alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)- -C-O-(C_1-C_6)alkyl, -C(=O)H, $-CH_2OR^{13}$, NH(C_1-C_6)alkyl-, -NHC(=O)H, $-NR^{24}$C-(C_1-C_6)alkyl and –NHC(=O)-(C_1-C_6)alkyl;

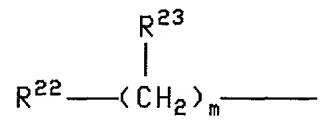
one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, (C_1-C_3)alkyl, (C_1-C_8)acyloxy(C_1-C_3)alkyl, (C_1-C_8)alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl, HC(=O)-, $R^{14}R^{15}NCO_2CH_2$-, $R^{16}OCO_2CH_2$-, (C_1-C_4)alkyl-CO_2CH_2-, -$CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2$-, $R^{19}OCO_2$-, $C_6H_5CH_2CO_2CH_2$-, $C_6H_5CO_2CH_2$-, (C_1-C_4)alkyl-CH(OH)-, C_6H_5CH(OH)-, $C_6H_5CH_2$CH(OH)-, CH_2halo, $R^{20}SO_2OCH_2$, $-CO_2R^{16}$ and $R^{21}CO_2$-;

R^{10} and R^{11} are independently selected from hydrogen, (C_1-C_3) alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula



wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond, and any

one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^{23} (as indicated by the slanted line to R^{23} which intersects the horizontal line to $(CH_2)_m$ in the above figure);

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, $(C_1$-$C_3)$alkyl and phenyl;

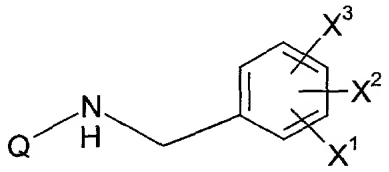
R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$-alkyl-O-C(=O)-, $(C_1$-$C_6)$alkyl-O-C(=O)-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-C(=O)- $(C_1$-$C_6)$alkyl-C(=O)-$(C_1$-$C_6)$alkyl-O-, $(C_1$-$C_6)$alkyl-C-, $(C_1$-$C_6)$-alkyl-C(=O)-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$ straight or branched alkyl, $(C_3$-$C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-$(C_2$-$C_6)$alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-$(C_2$-$C_6)$alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, $(C_1$-$C_6)$alkyl optionally substituted with from one to three fluorine atoms, $(C_1$-$C_6)$alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, amino, $(C_1$-$C_6)$-alkylamino, $(C_1$-$C_6)$alkyl-O-C(=O), $(C_1$-$C_6)$alkyl-O-C(=O)-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-C(=O)-O-, $(C_1$-$C_6)$alkyl-C(=O)-$(C_1$-$C_6)$alkyl-O-, $(C_1$-$C_6)$alkyl-C(=O)-, $(C_1$-$C_6)$alkyl-C-$(C_1$-$C_6)$alkyl-, di-$(C_1$-$C_6)$alkylamino, -C(=O)NH-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$-alkyl-C(=O)-NH-$(C_1$-$C_6)$alkyl, -NHC(=O)H and –NHC(=O)-$(C_1$-$C_6)$alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the proviso that when R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged.

8. A method of treating anxiety or depression in a mammal, comprising administering to said mammal an antianxiety effective amount or an antidepressant effective amount, respectively, of a pharmaceutical composition according to claims 1, 2, 3, 4, 5, 6, or 7.

9. A method of treating anxiety or depression in a mammal, comprising administering to said mammal: (a) a compound that exhibits activity as an anxiolytic antianxiety agent or an antidepressant, or a pharmaceutically acceptable salt thereof; and (b) a CNS-penetrant NK-1 receptor antagonist or pharmaceutically acceptable salt thereof; wherein the active agents "a" and "b" above are present in amounts that render the combination of the two agents effective in treating, respectively, anxiety or depression.

10. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula I, as depicted and defined below, and their pharmaceutically acceptable salts:

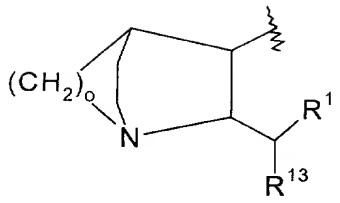


I

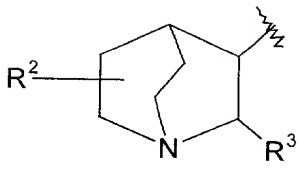
wherein X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6) alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and

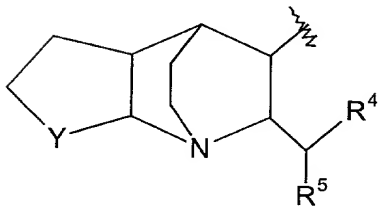
Q is a group of the formula



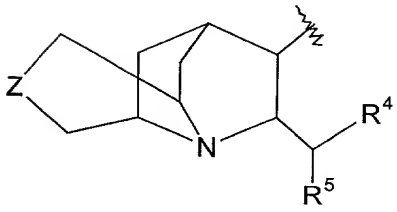
II



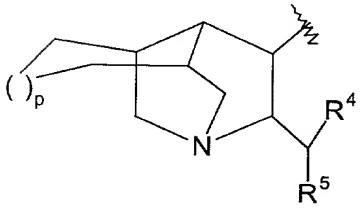
III



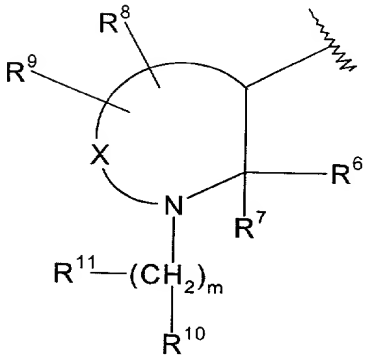
IV



V

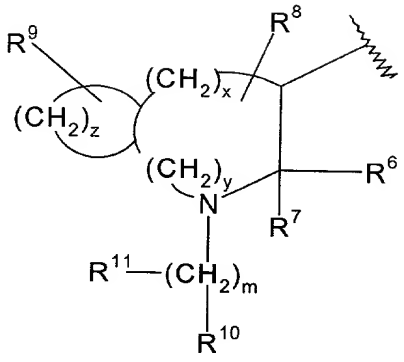


VI



VII

OR



VIII

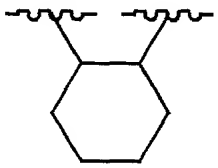
wherein R^1 is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

R^{13} is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^1;

R^2 is hydrogen or (C_1-C_6) alkyl;

R^3 is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R^3 may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



(J)

;

Z is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

o is two or three;

p is zero or one;

R^4 is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C_1-C_3) alkoxy-carbonyl and benzyloxycarbonyl;

R^5 is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^8, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^9;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{11};

R^6 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl,

furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl,(C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^7 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^6 and R^7, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^8 and R^9 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,-(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^6;

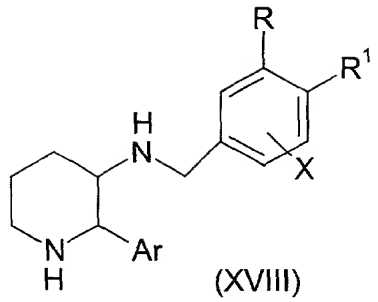
R^{10} is $NHCR^{12}$, $NHCH_2R^{12}$, $NHSO_2R^{12}$ or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9;

R^{11} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9; and

R^{12} is (C_1-C_6)alkyl, hydrogen, phenyl(C_1-C_6)alkyl or phenyl optionally substituted with (C_1-C_6) alkyl; and

with the proviso that (a) when m is 0, R^{11} is absent, (b) neither R^8, R^9, R^{10} nor R^{11} can form, together with the carbon to which it is attached, a ring with R^7, (c) when Q is a group of the formula VIII, R^8 and R^9 cannot be attached to the same carbon atom, and (d) when R^8 and R^9 are attached to the same carbon atom, then either each of R^8 and R^9 is independently selected from hydrogen, fluoro, (C_1-C_6) alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^8 and R^9, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached.

11. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XVIII, as depicted and defined below, and their pharmaceutically acceptable salts:



(XVIII)

wherein R is halo (C_1-C_8)alkyl, halo (C_2-C_8)alkenyl, halo (C_2-C_8)alkynyl or halo (C_1-C_8)alkyl substituted by hydroxy or (C_1-C_8)alkoxy; R^1 is hydrogen, halo or (C_1-C_6)alkoxy; or

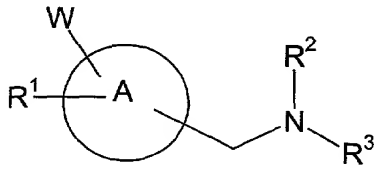
R and R^1, together with the two carbon atoms shared between the benzene ring and the R and R^1, complete a fused (C_4-C_6)cycloalkyl wherein one carbon atom is optionally replaced by oxygen and wherein one or two of the carbon atoms are optionally substituted by up to five subtituents selected from halo, (C_1-C_6)alkyl and halo (C_1-C_6)alkyl;

X is (C_1-C_6)alkoxy, halo (C_1-C_6)alkoxy, phenoxy or halo; and

Ar is phenyl optionally substituents by halo.

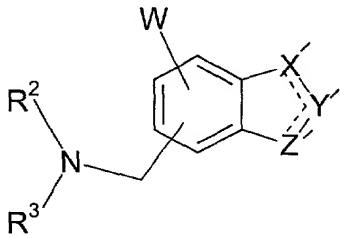
12. A method according to claim 11, wherein the NK-1 receptor antagonist is administered in an amount ranging from about 5 mg per day to about 200 mg per day.

13. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula IXa or IXb, as depicted and defined below, and their pharmaceutically acceptable salts:



IXa

or



IXb

wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the side chain containing NR^2R^3 is attached to a carbon atom of ring system A;

W is hydrogen, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, -$S(O)_v$-(C_1-C_6) alkyl wherein v is zero, one or two, halo, benzyloxy or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

R^1 is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazolyl or thiophenyl), wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from $(C_1\text{-}C_6)$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_6)$ alkoxy optionally substituted with from one to three fluorine atoms;

the dotted lines in formula Ib indicate that one of the X'-Y' and Y'-Z' bonds may optionally be a double bond;

X' is selected from =CH-, $-CH_2-$, -O-, -S-, -SO-, $-SO_2-$, $-N(R^4)-$, -NH-, =N-, $-CH[(C_1\text{-}C_6)\text{alkyl}]-$, $=C[(C_1\text{-}C_6)\text{alkyl}]-$, $-CH(C_6H_5)-$ and $=C(C_6H_5)-$;

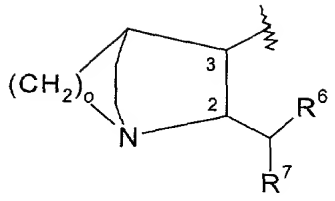
Y' is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2-$, $=C[(C_1\text{-}C_6)\text{alkyl}]-$, $-CH[(C_1\text{-}C_6)\text{alkyl}]-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, =N-, -NH-, $-N(R^4)-$, =C(halo)-, $=C(OR^4)-$, $=C(SR^4)-$, $=C(NR^4)-$, -O-, $=C(CF_3)-$, $=C(CH_2C_6H_5)-$, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)-$ and $-CH(C_6H_5)-$ may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of said $=[(C_1\text{-}C_6)\text{alkyl}]-$ and $-CH[C_1\text{-}C_6)\text{alkyl}]-$ may optionally be substituted with from one to three fluorine atoms;

Z' is selected from =CH-, $-CH_2-$, =N-, -NH-, -S-, $-N(R^4)-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, $=C[(C_1\text{-}C_6)$ alkyl$]-$ and $-CH[(C_1\text{-}C_6)\text{alkyl}]-$;

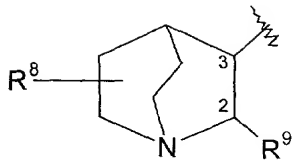
or X', Y' and Z', together with the two carbon atoms shared between the benzo ring and the X'Y'Z' ring, form a fused pyridine or pyrimidine ring;

R^2 is hydrogen or $-CO_2(C_1\text{-}C_{10})$alkyl;

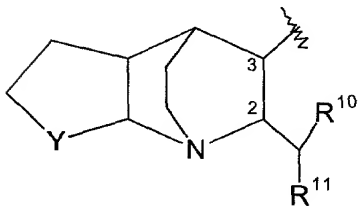
R^3 is selected from



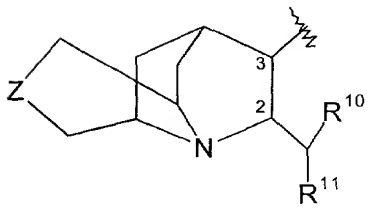
V



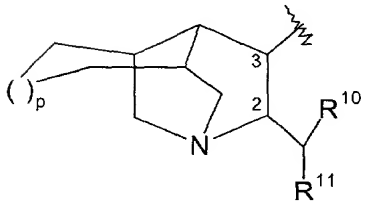
XI



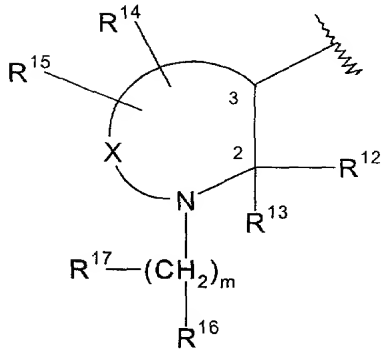
XII



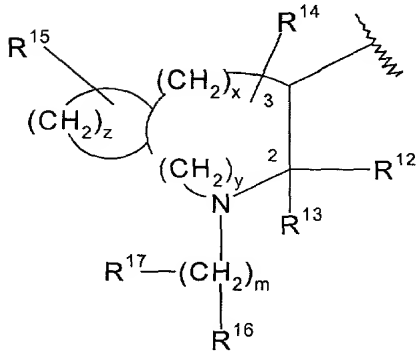
XIII



XIV

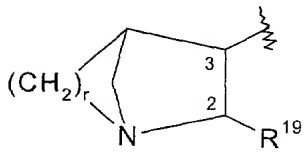


XV



XVI

and



XVII

wherein R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and

phenyl, wherein said phenyl may optionally be substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

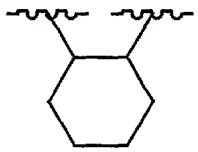
R^4 is (C_1-C_6) alkyl or phenyl;

R^7 is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^6;

R^8 is hydrogen or (C_1-C_6) alkyl;

R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



(J)

;

Z is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

x is zero, one or two;

y is zero, one or two;

z is three, four or five;

o is two or three;

p is zero or one;

r is one, two or three;

the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbon atoms of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom

of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};

R^{12} is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6) alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^{13} is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to such point of attachment may optionally be replaced by oxygen, nitrogen or sulfur;

R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C(=O)-OH, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^{12};

R^{16} is $NHC(=O)R^{18}$, $NHCH_2R^{18}$, SO_2R^{18}, CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};

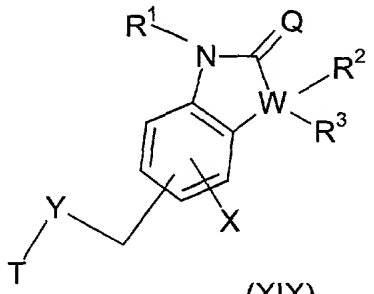
R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and

R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula XVI, R^{14} and R^{15} cannot be attached to the same carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, (C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl

and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} can not both be hydrogen, and (e) when R^{14} or R^{15} is attached to a carbon atom of X or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom.

14. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XIX, as depicted and defined below, and their pharmaceutically acceptable salts:



(XIX)

wherein

W is methylene, ethylene, propylene, vinylene, -CH_2-O-,-O-CH_2-, -CH_2-S- or -S-CH_2-;

R^1, R^2 and R^3 are independently hydrogen, (C_1-C_3) alkyl, (C_1-C_3) alkoxy or halo (C_1-C_3) alkyl, provided that when W is methylene, both R^2 and R^3 are not hydrogen;

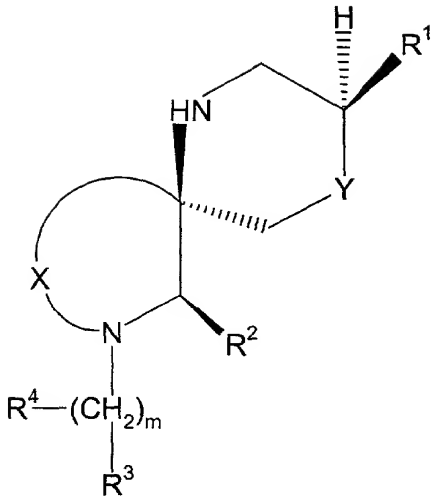
X is halo, (C_1-C_3) alkoxy, (C_1-C_3) alkoxy or (C_1-C_3) alkenyl;

Y is imino or oxy;

Q is oxygen or sulfur; and

T is (2S,3S)-2-diphenylmethylquinuclidin-3-yl,(2S,3S)-2-phenylpiperdin-3-yl or (2S,3S)-2-diphenylmethyl-1-azanorbornan-3-yl.

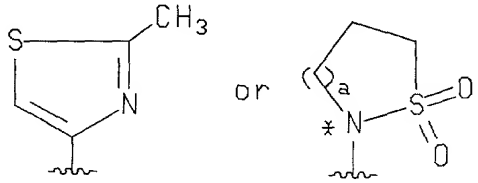
15. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XX, as depicted and defined below, and their pharmaceutically acceptable salts:



XX

wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, $(C_1\text{-}C_6)$-alkylamino, di-$(C_1\text{-}C_6)$alkylamino, -C(=O)-NH-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-C(=O)-NH-$(C_1\text{-}C_6)$ alkyl, hydroxy$(C_1\text{-}C_4)$alkyl,-NHC(=O)H, -NHC(=O)-$(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_4)$alkoxy$(C_1\text{-}C_4)$alkyl, -$S(O)_v$-$(C_1\text{-}C_{10})$-alkyl wherein v is zero, one or two, -$S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, -$SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, $(C_1\text{-}C_6)$alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, $(SO_2\text{-}(C_1\text{-}C_{10})$alkyl) $((C_1\text{-}C_{10})$alkyl)N wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, -N$(SO_2\text{-}(C_1\text{-}C_{10})$alkyl$)_2$ and $(SO_2$-aryl) $((C_1\text{-}C_{10})$alkyl)N; and wherein the aryl moieties of said -$S(O)_v$-aryl, -O-aryl and $(SO_2$-aryl) $((C_1\text{-}C_{10})$alkyl)N are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy and halo;

or R^1 is phenyl substituted with a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R^1;

R^2 is selected from $(C_1\text{-}C_6)$ straight or branched alkyl, $(C_3\text{-}C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from

biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;

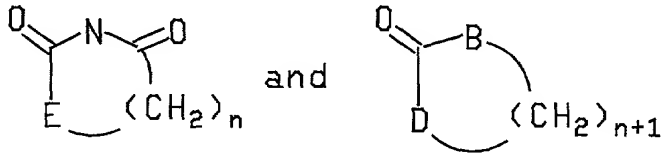
R^3 is selected from $NHC(=O)R^8$, $NHCH_2R^8$, SO_2R^8, AR^5, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;

A is CH_2, nitrogen, oxygen, sulfur or carbonyl;

R^8 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

R^4 is selected from oximino (=NOH) and the radicals set forth in the definitions of R^2, R^6 and R^7;

R^5 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said

$(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a $(C_3$-$C_5)$ fused carbocyclic ring;

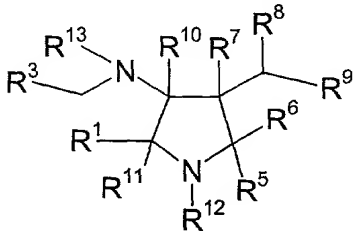
X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;

R^6 and R^7 are independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy, -C(=O)-OH, $(C_1$-$C_6)$alkyl-O-C(=O)-, $(C_1$-$C_6)$alkyl-O-C(=O)-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-C(=O)-O-, $(C_1$-$C_6)$alkyl-C(=O)-$(C_1$-$C_6)$alkyl-O-, $(C_1$-$C_6)$alkyl-C-, $(C_1$-$C_6)$alkyl-C(=O)-$(C_1$-$C_6)$alkyl- and the radicals set forth in the definition of R^2; and

Y is $(CH_2)_z$ wherein z is zero or one;

with the proviso that: (a) when A is $-(CH_2)-$ or carbonyl, R^5 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; and (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom.

16. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XXI, as depicted and defined below, and their pharmaceutically acceptable salts:



XXI

wherein R^1 is selected from hydrogen, $(C_1$-$C_6)$ straight or branched alkyl, $(C_3$-$C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl $(C_2$-$C_6)$ alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl $(C_2$-$C_6)$ alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, $(C_1$-$C_6)$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1$-$C_6)$ alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy), $(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkyl-O-C(=O)-, $(C_1$-$C_6)$alkyl-O-C(=O)- $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-C(=O)-O-, $(C_1$-$C_6)$alkyl-C-, $(C_1$-$C_6)$alkyl-O-, $(C_1$-$C_6)$alkyl-C(=O)-, $(C_1$-$C_6)$alkyl-C(=O)-, $(C_1$-$C_6)$alkyl-, di-$(C_1$-$C_6)$alkylamino, -C(=O)NH-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl-C(=O)-NH-$(C_1$-$C_6)$alkyl-,

-NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, phenyl, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6) alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)- -C-O-(C_1-C_6)alkyl, -C(=O)H, -CH_2OR^{13}, NH(C_1-C_6)alkyl-, -NHC(=O)H, -NR^{24}C-(C_1-C_6)alkyl and –NHC(=O)-(C_1-C_6)alkyl;

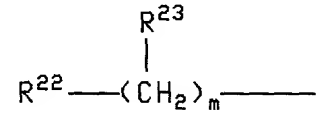
one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, (C_1-C_3)alkyl, (C_1-C_8)acyloxy(C_1-C_3)alkyl, (C_1-C_8)alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl, HC(=O)-, $R^{14}R^{15}NCO_2CH_2$-, $R^{16}OCO_2CH_2$-, (C_1-C_4)alkyl-CO_2CH_2-, -$CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2$-, $R^{19}OCO_2$-, $C_6H_5CH_2CO_2CH_2$-, $C_6H_5CO_2CH_2$-, (C_1-C_4)alkyl-CH(OH)-, $C_6H_5CH(OH)$-, $C_6H_5CH_2CH(OH)$-, CH_2halo, $R^{20}SO_2OCH_2$, -CO_2R^{16} and $R^{21}CO_2$-;

R^{10} and R^{11} are independently selected from hydrogen, (C_1-C_3) alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula



wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^{23} (as indicated by the slanted line to R^{23} which intersects the horizontal line to $(CH_2)_m$ in the above figure);

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)-alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)- (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)-alkyl-C(=O)-(C_1-C_6)alkyl, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-

C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O), (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the proviso that when R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged.

COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY

Abstract

The present invention relates to a method of treating depression or anxiety in a mammal, including a human, by administering to the mammal a CNS-penetrant NK-1 receptor antagonist (e.g., a substance P receptor antagonist) in combination with an antidepressant or an anxiolytic agent. It also relates to pharmaceutical compositions containing a pharmaceutically acceptable carrier, a CNS-penetrant NK-1 receptor antagonist and an anxiolytic agent or antidepressant.